Clinical Trial Protocol

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EU CT Number	2023-506369-79-00	
Universal Trial No.	U1111-1292-3392	
BI Trial No.	1403-0011	
BI Investigational Medicinal Product(s)	Brigimadlin (BI 907828)	
Title	Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours	
Lay Title	A study to test whether brigimadlin (BI 907828) helps people with cancer in the biliary tract, pancreas, lung, or bladder	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted]	
Coordinating Investigator		
Current Version and Date	Version 6.0, 04 Feb 2025	
Original Protocol Date	11 Jul 2022	**Page 1 of 136**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	11 Jul 2022
Revision date	04 Feb 2025
BI trial number	1403-0011
EU CT Number	2023-506369-79-00
Universal Trial Number	U1111-1292-3392
Title of trial	Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial
Clinical phase	Phase II
Trial rationale	The trial will investigate brigimadlin in the treatment of different locally advanced / metastatic, MDM2 amplified, TP53 wild-type solid tumours that are not suitable for targeted treatment and/or standard of care therapy. Treatment options for these patients are limited and often consist of several, subsequent chemotherapies that are not appropriate for many patients and show minimal efficacy. Brigimadlin is an orally available MDM2-p53 antagonist with a favourable benefit-risk assessment. The trial is designed to bring a new treatment faster to a patient population with a high unmet medical need.
Trial objective(s)	The trial will assess the efficacy, safety, and tolerability of brigimadlin monotherapy in multiple cohorts of patients with locally

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	advanced / metastatic, MDM2 amplified, TP53 wild-type solid tumours. Cohort 1 and Cohort 1-CN (China only) (biliary tract adenocarcinoma): • The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with objective response (OR). • Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS) as well as the assessment of health-related quality of life as assessed by the EORTC QLQ-C30 and the EORTC QLQ-BIL21. Cohort 2 (pancreatic ductal adenocarcinoma): • The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR. • Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS. Cohort 3 (lung adenocarcinoma): • The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR. • Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS. Cohort 4 (urothelial bladder cancer): • The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR. • Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS.
Trial endpoints	<u>Primary endpoint:</u> Objective response (OR) based on central independent review. OR is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 from the date of treatment start until the earliest date of disease progression, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent. <u>Secondary endpoints:</u> • DOR based on central independent review. DOR is defined as the time from first documented confirmed OR until the earliest date of disease progression or death among patients with confirmed objective response. • PFS based on central independent review. PFS is defined as the time from treatment start until the earliest date of tumour

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	progression according to RECIST version 1.1 or death from any cause, whichever occurs first. • OS, defined as the time from treatment start until death from any cause. • Disease control (DC) based on central independent review. DC is defined as a best overall response of CR, PR, or stable disease (SD) where best overall response is defined according to RECIST version 1.1. • Occurrence of treatment-emergent adverse events (AEs) during the on-treatment period. • Occurrence of treatment-emergent AEs leading to trial drug discontinuation during the on-treatment period. • Endpoints reflecting Patient Reported Outcomes (PRO) will be assessed with the following PRO measures (PROMs), for Cohort 1 only: o Change from baseline in EORTC QLQ-C30 physical functioning domain score o Change from baseline in EORTC QLQ-C30 fatigue domain score o Change from baseline in EORTC QLQ-C30 role functioning domain score o Change from baseline in EORTC QLQ-BIL21 tiredness domain score
Trial design	Open-label, single-arm, seamless Phase IIa/IIb trial
Total number of patients entered	The total number of patients for the entire trial is approximately 155 patients.
Number of patients per treatment group	Cohort 1 (biliary tract adenocarcinoma): Approximately 90 patients: 30 patients will be enrolled before the interim futility analysis; approximately 60 additional patients will be enrolled after the cut-off for the interim futility analysis. Recruitment will continue whilst the interim futility analysis is conducted. Cohort 1-CN (biliary tract adenocarcinoma, mainland China only): Approximately 25 patients: Recruitment will continue independently of the conduct and analysis of Cohort 1. Cohort 2 (pancreatic ductal adenocarcinoma): Approximately 10 patients. A futility analysis will be performed to assess the efficacy signal before deciding on the next steps.

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	Cohort 3 (lung adenocarcinoma): Approximately 15 patients. A futility analysis will be performed to assess the efficacy signal before deciding on the next steps. Cohort 4 (urothelial bladder cancer): Approximately 15 patients. A futility analysis will be performed to assess the efficacy signal before deciding on the next steps. **In November 2024, Boehringer Ingelheim decided to discontinue future development of brigimadlin. Recruitment in 1403-0011 and further expansion of the study, including Cohort-1-CN has been discontinued as of 26 Nov 2024.**
Diagnosis	Locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma (Cohort 1 and Cohort 1-CN), locally advanced / metastatic, MDM2 amplified, TP53 wild-type pancreatic ductal adenocarcinoma (Cohort 2), locally advanced / metastatic, MDM2 amplified, TP53 wild-type lung adenocarcinoma (Cohort 3), locally advanced / metastatic, MDM2 amplified, TP53 wild-type urothelial bladder cancer (Cohort 4).
Main inclusion and exclusion criteria	Main inclusion criteria: • Diagnosis of a solid tumour which meets the criteria for an open trial cohort: o Cohorts 1 and 1-CN (biliary tract adenocarcinoma): Locally advanced or metastatic biliary tract adenocarcinoma (intra- and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer). Patient must have received appropriate prior standard of care therapy; or (in the opinion of the investigator) patient is unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. o Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, urothelial bladder cancer): Locally advanced or metastatic pancreatic ductal adenocarcinoma/lung adenocarcinoma/urothelial bladder cancer. Patient must have received appropriate prior standard of care therapy. • Written pathology report / molecular profiling report indicating MDM2 amplification and TP53 wild-type status. • Archival tissue (formalin fixed paraffin embedded [FFPE] tumour blocks or slides) must be provided for retrospective confirmation of MDM2 amplification and TP53 status. • Presence of at least 1 measurable target lesion according to RECIST version 1.1. • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

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	• Adequate organ function. Main exclusion criteria: • Previous administration of brigimadlin or any other MDM2-p53 or MDMX (MDM4)-p53 antagonist. • Active bleeding, significant risk of haemorrhage (e.g. previous severe gastrointestinal bleeding, previous haemorrhagic stroke at any time), or current bleeding disorder (e.g. haemophilia, von Willebrand disease). • Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to start of trial treatment or planned within 6 months after screening (e.g. hip replacement). • Clinically significant previous or concomitant malignancies in the opinion of the investigator affecting the efficacy and/or outcome of the trial. • Patients who must or intend to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial. • Receiving treatment for brain metastases or leptomeningeal disease (LMD) which may interfere with safety and/or efficacy endpoint assessment.
Test product	Brigimadlin
dose	[redacted]
mode of administration	Oral
Comparator product(s)	Not applicable
Duration of treatment	Treatment will be administered until documented disease progression, unacceptable toxicity, withdrawal of consent, or other reasons requiring treatment discontinuation. Treatment beyond progression will be allowed if the investigator judges that this would provide continued clinical benefit to the patient.
Statistical methods	Cohort 1 (biliary tract adenocarcinoma): The main objective will be evaluated by 2 statistical objectives: Statistical objective 1 is to show superiority of brigimadlin monotherapy over historical benchmark from current available treatment options using ORR. Statistical objective 2 is to show definitive clinically meaningful efficacy of brigimadlin monotherapy using ORR. The primary endpoint OR will be assessed at

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	2 timepoints: (1) at the interim futility analysis when the first 30 treated patients have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier; and (2) at the final primary endpoint analysis when all treated patients (approximately 90 patients) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier. The primary endpoint OR will be analysed in terms of confirmed ORR (based on central independent review), defined as the proportion of patients with a best overall response of CR or PR. A non-binding futility boundary of confirmed ORR = 20% is planned for the interim futility analysis. For the final primary endpoint analysis of statistical objective 1, a statistical testing of ORR against the null hypothesis (ORR = 5%) based on the binomial distribution will be conducted and the corresponding p-value will be calculated. This p-value will be compared with a significance level of 2.5% to claim success for statistical objective 1. The observed ORR together with a 95% confidence interval will be provided as well. For the final primary endpoint analysis of statistical objective 2, the observed ORR will be compared with a pre-specified critical value of 23.3% (21/90) to claim success for statistical objective 2. The secondary endpoints DOR, PFS, and DC will be evaluated at the same time as the final primary endpoint analysis. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohort 1. No formal testing is planned for secondary endpoints. Cohort 1-CN (biliary tract adenocarcinoma): For the primary endpoint OR, the proportion of patients with a best overall response of CR or PR will be analysed when all treated patients in this cohort (approximately 25 patients) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier. When all these patients are evaluable for ORR, the observed ORR will be analysed. Proportions will be presented with 95% CIs (exact method). Cohort 2 (pancreatic ductal adenocarcinoma): For the primary endpoint OR, the proportion of patients with a best overall response of CR or PR will be analysed after approximately 10 patients have been followed for at least 12 weeks (or 2 post-baseline assessments) or have discontinued tumour assessment earlier. When all these patients are evaluable for ORR, the observed ORR will be analysed. Proportions will be presented with 95% CIs (exact method).

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	The secondary endpoints DOR, PFS, and DC will be evaluated at the same time as the final primary endpoint analysis. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohort 2. No formal testing is planned for Cohort 2. Cohorts 3 and 4 (lung adenocarcinoma/urothelial bladder cancer): For the primary endpoint OR, the proportion of patients with a best overall response of CR or PR will be analysed after approximately 15 patients have been followed for at least 12 weeks (or 2 post-baseline assessments) or have discontinued tumour assessment earlier. When all these patients are evaluable for ORR, the observed ORR will be analysed. Proportions will be presented with 95% CIs (exact method). The secondary endpoints DOR, PFS, and DC will be evaluated at the same time as the final primary endpoint analysis. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohorts 3 and 4. No formal testing is planned for Cohorts 3 and 4.

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FLOWCHART

Reduced schedule flowchart brigimadlin treatment / Trial 1403-0011 (as of Global Amendment 5)

Trial period	**Treatment cycle [1] (Cycle X)**	**End of treatment (EOT)**	**FU for safety [2]**
Timing	**Day 1 [3]** (±3 d)	**Within 7 days of EOT decision [2]**	**30 to 35 days after the last dose**
Re-consent	X[4]		
Physical examination and vital signs [5]	X	X	X
Eastern Cooperative Oncology Group (ECOG) Performance Status	X	X	X
Safety laboratory blood tests (haematology, biochemistry, and coagulation) and urinalysis	X	X	X
Pregnancy test [6]	X	X	X [6]
Single 12 lead-electrocardiogram (ECG)	X [7]	X	X
Tumour assessment [8]	Patients will have scans every 6 weeks (±7 days) until 36 weeks after the first dose of brigimadlin received and then every 12 weeks until progression or EOT, whichever occurs first		
Assess eligibility for further treatment [9]	X		
Brigimadlin administration	X		
Adverse events	X	X	X
Concomitant therapies	X	X	X
Completion of patient participation			X[10]

1. A cycle is 21 days (±3 days) in duration and may be extended if subsequent dosing is delayed. An interval of 18 to 24 days between doses must be maintained throughout, unless criteria for delaying treatment are met. Patients may continue on treatment for unlimited cycles, until criteria for stopping treatment are met (see Section 3.3.4.1).
2. If the decision to permanently discontinue trial treatment is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit, see Section 3.3.4.
   If the decision to permanently discontinue is made >35 days after dosing (i.e. following a dose delay) the FU for Safety visit will take place as soon as possible but will be >35 days after last dose. In this situation the EOT visit and the FU for Safety visit may be combined.
   If a patient receives brigimadlin in another clinical trial, safety follow-up in this trial will end, and safety follow-up will continue uninterrupted in the new trial.
3. Day 1 assessments may be performed within 72 hours prior to the administration of treatment and where applicable results must be available to assess eligibility to receive further treatment.
4. Patients will re-consent to changing from the original flowchart to this flowchart prior to the first treatment cycle starting after Global Amendment 5.
5. Physical examination and vital signs include weight, temperature, heart rate, and blood pressure. Additional physical examinations including vital signs may be conducted as clinically indicated at the investigator's discretion. Refer to Sections 5.2.1and 5.2.2.
6. A serum or urine pregnancy test must be performed prior to administration of treatment on Day 1 of every cycle, at EOT, and then monthly until 6 months after the last dose of treatment. During follow-up, pregnancy testing may be performed remotely, no further visits are planned after FU for safety.
7. A single 12-lead ECG will be performed Cycles 1-5, Cycle 8, Cycle 11, and every 6th cycle thereafter.
8. The imaging schedule will be independent of treatment cycles and will be conducted until confirmation of objective disease progression by investigator assessment or EOT, whichever occurs first. The tumour assessment schedule should not change for any reason, including interruption / delay of treatment.
9. Assessment of eligibility to receive further treatment is performed prior to dosing at every cycle.
10. End of Study (corresponds with individual patient's End of Trial).

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Flowchart brigimadlin treatment / Trial 1403-0011 (no longer applicable as of Global Amendment 5)

Brigimadlin / Trial 1403-0011	**Screening**	**Cycles 1 and 2** [1]			**Cycles 3 and 4** [1]		**Cycle ≥5** [1]	**EOT** [2]	**FU for safety** [2]	**FU for PD** [3]	**FU for survival** [4]
Time point	Day -28 to -1	Day 1 (±3 d at C2)	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (±3 d)	Day 15 (± 2 d)	Day 1 (±3 d)	Within 7 d of EOT decision	30-35 d after last dose	Every 6 (12) weeks (±7 d)	Every 12 weeks (±7 d)
Informed consent [5]	X										
Review of inclusion / exclusion criteria [6]	X										
Demographics	X										
Medical history	X										
Oncological history	X										
HBV and HCV testing	X										
Archival tumour material [7]	X										
Physical examination [8]	X	X	X	X	X	X	X	X	X	X	
Vital signs [8]	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	X	
Haematology (safety laboratory) [9]	X	X	X	X	X	X	X	X	X	(X)	
Biochemistry (safety laboratory) [9]	X	X	X	X	X	X	X	X	X	(X)	
Coagulation (safety laboratory) [9]	X	X			X		X	X	X	(X)	
Urinalysis (safety laboratory) [9]	X	X			X		X	X	X	(X)	
Pregnancy test [10]	X	X			X		X	X	X [10]	X [10]	X [10]
Single 12-lead ECG [11]	X	X			X		X [19]	X	X		
Blood sample for PK analysis of brigimadlin [12]		X	X	X(C1)	X		X [19]				
Plasma samples for ctDNA [13]		X			X		X	X			
Plasma samples for miRNA [13]		X			X		X	X			
Plasma samples for circulating proteins – for all cohorts except for Cohort 1-CN [13]		X			X		X	X			
Whole blood sample for pharmacogenetics [13]		X(C1)									
Blood sample for GDF-15 [13]		X	X	X(C1)	X		X [19]	X			
Blood sample for cancer antigen (CA)19-9 [13]		X			X		X	X			

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Brigimadlin / Trial 1403-0011	**Screening**	**Cycles 1 and 2** [1]			**Cycles 3 and 4** [1]		**Cycle ≥5** [1]	**EOT** [2]	**FU for safety** [2]	**FU for PD** [3]	**FU for survival** [4]
Time point	Day -28 to -1	Day 1 (±3 d at C2)	Day 8 (± 1 d)	Day 15 (± 1 d)	Day 1 (±3 d)	Day 15 (± 2 d)	Day 1 (±3 d)	Within 7 d of EOT decision	30-35 d after last dose	Every 6 (12) weeks (±7 d)	Every 12 weeks (±7 d)
Blood sample for carcinoembryonic antigen (CEA) [13]		X			X		X	X			
PROM: EORTC QLQ-C30 and EORTC IL46 (item 168) [14]		From C1D1 until EOT every 3 weeks (±2 days); at EOT; 6 weeks (±2 days) and 12 weeks (±2 days) after EOT									
Cohorts 1 and 1-CN only: EORTC QLQ-BIL21		From C1D1 until EOT every 3 weeks (±2 days); at EOT; 6 weeks (±2 days) and 12 weeks (±2 days) after EOT									
Cohort 2 only: EORTC QLQ-PAN26		From C1D1 until EOT every 3 weeks (±2 days); at EOT; 6 weeks (±2 days) and 12 weeks (±2 days) after EOT									
Cohort 3 only: NSCLC-SAQ		From C1D1 until EOT every 3 weeks (±2 days); at EOT; 6 weeks (±2 days) and 12 weeks (±2 days) after EOT									
PROM: PGIS, PGIC [14]		From C1D1 until EOT every 12 weeks (±2 days); at EOT									
Concomitant therapy [15]	X	X	X	X	X	X	X	X	X	X	X
Adverse events [16]	X	X	X	X	X	X	X	X	X	X	X
Brigimadlin administration [17]		X			X		X				
Tumour assessment [18]	X	Every 6 weeks (± 7 days) starting 6 weeks after C1D1 and continuing until disease progression. From Week 48 onwards every 12 weeks ±7 days.									
Termination of brigimadlin								X			
Fresh tumour biopsy (optional) – for all cohorts except for Cohort 1-CN								X			
Patient status [4]											X

1. A cycle is 21 days (±3 days) in duration and may be extended if subsequent dosing is delayed e.g. due to toxicity. An interval of 18-24 days between doses must be maintained throughout, unless criteria for delaying treatment are met. Patients may continue treatment until any criteria for stopping medication are met (see Section 3.3.4.1).
2. EOT = End Of Treatment. All patients should undergo the EOT visit as soon as possible after permanent discontinuation of brigimadlin (within 7 days of the decision to stop treatment). If the decision to permanently discontinue brigimadlin is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit, see Section 3.3.4. After the EOT visit, the investigator should report only any cancers of new histology, trial drug related SAEs, and trial drug related AESIs, see Section 5.2.6.2.1.
   If the decision to permanently discontinue is made >35 days after dosing (i.e. following a dose delay) the FU for Safety visit will take place as soon as possible but will be >35 days after last dose. In this situation the EOT visit and the FU for Safety visit may be combined.

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3. For patients who discontinue for a reason other than confirmed disease progression by investigator assessment, follow-up visits continue until confirmed disease progression by investigator assessment, lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6. The frequency of follow-up visits is the same as the tumour assessment, i.e., every 6 weeks until week 48 and every 12 weeks thereafter.
4. During follow up for survival, patient visits to the clinic are not required. Information may be collected from the patient notes, via telephone contact or through an edevice for PROMs. Patient status will be collected until death, lost to follow-up, withdrawal of consent, or the end of the whole trial.
5. Written informed consent must be obtained before any protocol-specific screening assessments are performed. Re-consenting may become necessary when new relevant information becomes available.
6. C1D1 assessments (i.e. physical examination, ECOG performance status, vital signs, ECG, safety laboratory blood tests, urinalysis, pregnancy test, weight) can be skipped if they had been performed during screening within 72 h prior to C1D1 and in the opinion of the investigator a repeat is not required. In this case the latest value prior to start of treatment will be considered the baseline. At subsequent Day 1 visits, the assessments may be performed within 72 hours prior to the administration of treatment and where applicable results must be available to assess eligibility to receive further treatment.
7. Archival tumour tissue MUST be provided for all patients to retrospectively confirm MDM2 amplification and TP53 wild-type status. See Section 5.4.2 for details.
8. Physical examination and vital signs include height, weight, temperature, heart rate, and blood pressure. Additional physical examinations including vital signs may be conducted as clinically indicated at the investigator's discretion. Refer to Sections 5.2.1 and 5.2.2.
9. Safety laboratory assessments including haematology, serum biochemistry, coagulation, and urinalysis will be performed locally. Refer to Section 5.2.3. All safety laboratory tests can be repeated at any other time point, if clinically indicated, at the investigator's discretion.
10. A serum pregnancy test is mandatory for female patients of childbearing potential at screening. A serum or urine pregnancy test must be performed within 72 hours prior to administration of treatment on Day 1 of every cycle and at EOT. After EOT, pregnancy testing will be performed monthly until 6 months after the last dose of treatment, and it may be performed remotely. Refer to Sections 5.2.3 and 4.2.2.3 regarding restrictions for women of childbearing potential.
11. Electrocardiogram (ECG): Standard 12-lead (I, II, III, aVR, aVL, aVF, V1 - V6) resting ECGs will be recorded (detailed timing see Appendix 10.2). Refer to Section 5.2.4. ECGs may be repeated as clinically indicated.
12. A more detailed overview of PK sample collection can be found in Appendix 10.2. Please note that Day 15 sampling applies only for Cycle 1.
13. Blood samples for the biomarker analysis are mandatory. Details of blood sampling for all biomarker analyses are described in Section 5.4 and the detailed sampling schedule for PK and GDF-15 is available in Appendix 10.2. For all other biomarkers, sampling must be done at the day of the visit, ideally before drug administration.
14. PROM = Patient Reported Outcome Measures; QLQ = Quality of Life Questionnaire; PGIS = Patient Global Impression of Severity; PGIC = Patient Global Impression of Change.
    Patients may complete the assessments either on provided edevices or access to PROMs/QoL remotely with their own devices. Patients are not required to attend the clinic on non-dosing days to complete the questionnaires. On clinic days, it is recommended that patients complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status.
    Please note that the PGIC assessment is not required at C1D1.
15. For concomitant therapy and restrictions on concomitant therapy, refer to Sections 4.2.1 and 4.2.2.1.

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16. Adverse events: includes the review of safety laboratory tests if applicable. For details on AE reporting after treatment discontinuation, refer to Sections 5.2.6.2 and 6.2.3. Early and proactive management of side effects is essential to retention. The site is recommended to call the patient a few days after starting treatment to discuss whether the patient has side effects and how these can be treated. In addition, phone calls at any time are recommended e.g. in case of severe myelosuppression. The patients should be instructed to contact the sites if applicable.
17. Brigimadlin will be dispensed on Day 1 of each cycle by the investigator or an authorised designee. Refer to Section 4.3.
18. Tumour assessments performed prior to the informed consent as part of routine clinical practice will be accepted if they meet the requirements of the clinical trial protocol and are performed within the screening visit window.
    The imaging schedule will be independent of treatment cycles and will be conducted until confirmation of objective disease progression by investigator assessment for all patients (every 6 weeks until Week 48, every 12 weeks thereafter). The tumour assessment schedule should not change for any reason, including interruption / delay of treatment.
    Tumour assessments must be performed according to RECIST 1.1 and should include imaging of all known or suspected site of disease using an appropriate method (e.g. CT scan, MRI, ultrasound), as well as a brain scan at screening. The same method of assessment and the same imaging technique must be used at each subsequent timepoint to characterise each reported lesion throughout treatment and during follow-up. Photo documentation of superficial lesions should be provided.
    All imaging scans / timepoints must be submitted for central independent review. Refer to Section 5.1 and the imaging manual for additional details.
19. ECG, blood sampling for PK, and blood sampling for GDF-15 are performed in Cycle 5, cycle 8, cycle 11 and every 6th cycle thereafter.

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ABBREVIATIONS AND DEFINITIONS

[redacted]

ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine aminotransferase

[redacted]

aPTT	Activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
AST	Aspartate aminotransferase
$AUC_{0\text{-}tz}$	Area under the plasma concentration-time curve over the time interval from 0 to the last quantifiable data point
BCRP	Breast cancer resistance protein
BI	Boehringer Ingelheim
BLQ	Below the limit of quantitation
BLRM	Bayesian logistic regression model
BTC	Biliary tract adenocarcinoma
CA	Competent authority
CD4	Cluster of differentiation 4
CDx	Companion diagnostics
CEA	Carcinoembryonic antigen
CI	Confidence interval
CK	Creatinine kinase
CKD-EPI	Chronic kidney disease epidemiology
Cmax	Maximum plasma concentration
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRP	C-reactive protein
CSF	Colony-stimulating factor
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumour DNA
CTR	Clinical trial report

[redacted]

DBL	Database lock
DC	Disease control

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DDI	Drug-drug interaction
DHEA	Dehydroepiandrosterone
DILI	Drug induced liver injury
DLP	Data lock point
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form, paper or electronic
EDC	Electronic data capture
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (corresponds with End of Trial)
EOT	End of treatment
ESA	Erythropoietin-stimulating agent
ESMO	European Society for Medical Oncology
EUA	Emergency use authorisation
Eudra CT	European Union Drug Regulating Authorities Clinical Trials Database
EWOC	Escalation with overdose control
FDA	Food and drug administration
FFPE	formalin-fixed paraffin-embedded tissue
FU	Follow-up
FU-OS	Follow-up for overall survival
FU-PD	Follow-up for progressive disease
GCP	Good Clinical Practice
GDF-15 (MIC-1)	Growth differentiation factor 15 (macrophage inhibitory cytokine-1)
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IDMS	Isotope dilution-mass spectrometry
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional Review Board

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IRT	Interactive response technology
ISF	Investigator Site File
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LAG3	Lymphocyte-activation gene 3
LC/MS	Liquid chromatography-mass spectrometry
LMD	Leptomeningeal disease
LPLT	Last patient last treatment
LUAD	Lung adenocarcinoma
MASCC	Multinational association of supportive care in cancer
MDM2	Murine double minute 2
[redacted]	
MedDRA	Medical Dictionary for Drug Regulatory Activities
miRNA	Micro RNA
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NCCN	National Comprehensive Cancer Network
[redacted]	
NOA	Not analyzed
NOR	No valid result
NOS	No sample
NTI	Narrow therapeutic index
NYHA	New York Heart Association
[redacted]	
OPU	Operative unit
ORR	Objective response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PDAC	Pancreatic ductal adenocarcinoma
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
P-gp	Permeability glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PR	Partial response
PRO	Patient-reported outcome

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PROM	Patient-reported outcome measure
PS	Performance status
PT	Prothrombin time
QLQ	Quality of Life Questionnaire
QoL	Quality of life
QTcF	Corrected QT interval by Fredericia
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual effect period
RNA	Ribonucleic acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus type 2
SC	Steering committee
SD	Stable disease
SITC	Society for Immunotherapy of Cancer
SNP	Single nucleotide polymorphism
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reactions
TIC	Trial identification card
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TP53	Tumour protein p53
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
β-HCG	Beta human chorionic gonadotropin

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1. INTRODUCTION

In November 2024, Boehringer Ingelheim decided to discontinue future development of brigimadlin. No new safety concerns of brigimadlin have been observed and the overall benefit risk assessment of brigimadlin remains unchanged.

This section summarizes the changes implemented in Global Amendment 5. Recruitment in 1403-0011 and further expansion of the study, including Cohort-1-CN has been discontinued as of 26 Nov 2024. Patients still on treatment can continue to receive treatment in accordance with the reduced schedule Flowchart. Patients will be transferred to receive treatment through an alternative method (e.g. a rollover trial) wherever possible and available, please refer to Section 3.3.4.1. After all patients have ended treatment in this trial and completed the safety follow-up period, the final analysis will be performed.

All available primary and secondary endpoints will be reported in the final analysis in CTR. Further endpoints will not be analyzed. Hypothesis testing will no longer be conducted as a result of the decision to discontinue development of brigimadlin.

The assessment of efficacy will continue as described in Section 5.1, except all imaging-related endpoints will no longer be assessed by central independent review.

Patients will be followed up for safety as described in Section 5.2 but will no longer be followed up for disease progression and overall survival.

Sampling and analyses for pharmacokinetics of brigimadlin, exploratory analyses of biomarkers, and patient-reported outcome questionnaires will be discontinued. Samples that were already collected but not yet analysed will be destroyed.

1.1 MEDICAL BACKGROUND

Patients with locally advanced or metastatic biliary tract cancers as well as patients with many other solid tumours will succumb to their disease, justifying the substantial need for novel therapeutic strategies to improve their outcome. Targeted therapies are only available for few patients. Available data clearly demonstrate anti-tumour activity of MDM2-p53 antagonists as single agents in MDM2 amplified and TP53 wild-type tumours through reactivation of the tumour suppressor gene TP53 and, potentially, an immune-modulatory effect in line with the reported broad role of TP53 in immune responses via different mechanisms [R18-2217; R20-3567; R20-3570].

MDM2 amplification and TP53 wild-type has been reported in up to 6% of patients with biliary tract cancer, 0.8% for pancreatic ductal adenocarcinoma, 4.2% in lung adenocarcinoma, and 7.2% for bladder cancer. The trial will enrol patients with advanced and/or metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma (BTC) (Cohort 1 and Cohort 1-CN), patients with advanced and/or metastatic, MDM2 amplified, TP53 wild-type pancreatic ductal adenocarcinoma (PDAC) (Cohort 2), patients with advanced and/or metastatic, MDM2 amplified, TP53 wild-type lung adenocarcinoma (LUAD) (Cohort 3), patients with advanced and/or metastatic, MDM2 amplified, TP53 wild-type urothelial bladder cancer (Cohort 4), and patients with advanced and/or metastatic,

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MDM2 amplified, TP53 wild-type selected solid tumours for which efficacy signals have been reported from the ongoing brigimadlin Phase Ia/b Trials 1403-0001 and 1403-0002. Cohorts of specific tumour indications will be added based on evolving Phase Ib data.

The combination durvalumab, or pembrolizumab in certain circumstances, with gemcitabine + cisplatin chemotherapy is the standard 1st line treatment for patients with BTC [R24-1181; R23-1555]. The benefit of 2nd line FOLFOX chemotherapy is modest, with an mOS of 6 months, a median progression-free survival (mPFS) of 4 months, and an objective response rate (ORR) of 5% as shown in the ABC-06 trial, which recruited in the UK [R22-0948]. A randomized Korean Phase II trial showed an mOS of 6.3 months, a mPFS of 2.8 months, and an ORR of 5.9% [R24-0991].

Currently, patients with pancreatic ductal adenocarcinoma receive 1st line chemotherapy (FOLFIRINOX or nab-paclitaxel + gemcitabine), and 2nd line chemotherapy if the patient's condition allows. The benefit of 2nd line chemotherapy is modest, with a median overall survival (OS) of ~6 months and an ORR of 16% for the NAPOLI-regimen after gemcitabine-based 1st line treatment; the limited available data for gemcitabine + nab-paclitaxel after FOLFIRINOX indicate a similar outcome [R22-1698]. Gemcitabine or fluoropyrimidine-based regimens + oxaliplatin resulted in a median PFS of 3.1 months, a median OS of 5-7 months and an ORR <5% [R22-1697].

Patients with advanced/metastatic lung adenocarcinoma receive depending on their molecular profile targeted therapy such as EGFR-TKIs, checkpoint inhibitors +/- chemotherapy, and chemotherapy (platinum-doublet, but also in combination with anti-angiogenic substances, or as monotherapy). However, eventually patients run out of treatment options (≥ 3rd line, depending on alteration/s and prior therapies). Monotherapy with chemotherapy (e.g., docetaxel) in 2nd or later lines results in mOS of around 9 months, a PFS of 3-4 months, and ORR around 13%. [R16-5828, R14-3261, R16-1875].

NCCN explicitly recommends participation in clinical trials of new agents for patients with bladder cancer after first-line progression. Therapy options in second-line chemotherapy comprise (depending on first-line treatment and patient's condition) checkpoint inhibitors, chemotherapy, and enfortumab-vedontin. Median overall survival in second-line is 5-9 months, with enfortumab-vedontin up to 13 months, median PFS 4-6 months, and ORR of around 18%, with enfortumab 41% [R22-4068, R22-4066].

The ongoing brigimadlin trials: 1403-0001 (Phase Ia/b monotherapy trial) and 1403-0002 (combination of brigimadlin and ezabenlimab [an anti-PD-1 inhibitor]) have demonstrated positive efficacy signal in the 2L+ setting in patients with advanced BTC, PDAC, LUAD, and urothelial cancer. As of Feb 2024:

- BTC: a total of 26 patients were treated; 10 patients had a PR and 10 patients had a SD as best response.
- PDAC: a total of 3 patients were treated; 1 patient had a confirmed PR, and 1 patient had a SD.
- LUAD: a total of 13 patients were treated; 1 patient had a confirmed PR, and 8 patients had a SD.
- Urothelial cancer: a total of 7 patients were treated; 2 patients had a confirmed PR, and 4 patients had a confirmed SD.

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1.2 DRUG PROFILE

Mode of action

- The MDM2-p53 antagonist brigimadlin (also known as BI 907828) is a small molecule that binds the mouse double minute 2 homolog protein (MDM2) and inhibits its interaction with the tumour suppressor p53. Inhibition of this protein-protein interaction leads to stabilization of p53 followed by target gene induction, which results in cell cycle arrest or apoptosis in tumours with p53 wild-type status. For further details please refer to the Investigator's Brochure (IB) [c15936970].

Key pharmacokinetic characteristics



Drug interactions



For further details on brigimadlin drug interactions and restrictions regarding concomitant treatment, please refer to Section 4.2.2.1.

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Residual effect period

The Residual Effect Period (REP) is the period after the last administration of trial medication with measurable drug levels and/or pharmacodynamics effects still likely to be present. The REP for brigimadlin is 30 days.

Data from nonclinical studies

Nonclinical data suggest that the anti-tumour activity of brigimadlin in tumours harboring wildtype TP53 is based on a direct anti-tumour activity via activation of p53 function and induction of apoptosis in cancer cells, and an immunomodulatory activity, with synergistic efficacy in combination with immune checkpoint inhibitors targeting PD-1. Detailed non-clinical results are available in the IB [c15936970] and show that brigimadlin is a potent MDM2-p53 antagonist with a dose-linear PK, and a high bioavailability in several species. Available data support clinical investigation of brigimadlin in various malignancies with TP53 wild-type status, including tumours with MDM2 amplification.

Genotoxicity studies showed that brigimadlin was not mutagenic in the bacterial reverse mutation (Ames) test; but was clastogenic in the *in vitro* chromosomal aberration test. It was negative in the rat bone marrow assay, but induced DNA damage in the liver and duodenum of rats as assessed by the comet assay.

Data from clinical studies

There are currently several ongoing trials of brigimadlin in patients with advanced or metastatic solid tumours. These include the following:

- Trial 1403-0001 is a Phase Ia/Ib, open-label, multi-centre, dose-escalation study of brigimadlin monotherapy.
- Trial 1403-0002 is a Phase Ia/Ib, open-label, dose-escalation study of the combination of brigimadlin with ezabenlimab.
- 1403-0007 is a Phase 0/Ia trial in newly diagnosed glioblastoma.
- Trial 1403-0008 is a Phase II/III open-label trial of brigimadlin versus doxorubicin as 1st line therapy for dedifferentiated liposarcoma.
- Trial 1403-0019 is a Phase III trial in dedifferentated liposarcoma.

At the data lock point (DLP, 16 September 2023) of the current IB, more than 390 patients have received brigimadlin as monotherapy or in combination with ezabenlimab (anti-PD-1 mAb) with or without BI 754111 (LAG-3). An additional 389 patients had been treated with brigimadlin or doxorubicin in a blinded fashion in Trial 1403-0008 (Brightline-1).

The most frequent AEs observed were nausea, fatigue, thrombocytopenia, neutropenia, vomiting, anaemia, decreased appetite, and diarrhoea. The haematological AEs were generally reversible and Grade 3 or higher haematological events were manageable with appropriate treatment and dose modification.

For a more detailed description of the brigimadlin profile, please refer to the current IB [c15936970].

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1.3 RATIONALE FOR PERFORMING THE TRIAL

The trial will investigate brigimadlin monotherapy in different locally advanced / metastatic cancer types that are not suitable for targeted treatment and/or standard of care. Treatment options for these patients are limited and often consist of several, subsequent chemotherapies that are not appropriate for many patients and show minimal efficacy. Therefore, a treatment with a better efficacy and a manageable safety profile is needed.

Brigimadlin is an orally available MDM2-p53 antagonist with a favourable benefit-risk assessment based upon the ongoing clinical trials. Myelosuppression and gastrointestinal AEs were identified as the main treatment-induced side effects.

Patients in mainland China are enrolled in a separate cohort (Cohort 1-CN) because separate analyses are required for mainland China and rest of the world populations. A separate CDx development will be pursued for mainland China, as it is not feasible to export human tissue samples from China to the appointed global laboratory for CDx development. Instead, a laboratory located in China will perform the central laboratory analyses for patients enrolled in China (confirmation of MDM2 and TP53 status).

To bring new treatments faster to a patient population with a high unmet medical need, a seamless trial design is proposed.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

MDM2-p53 antagonists provide the opportunity to target the key tumour suppressor p53 (tumour protein p53). Brigimadlin is a tumour-targeting agent that leads to p53 activation, which triggers cell cycle arrest or apoptosis in cancer cells. Pharmacology data support that the compound can also modulate the immune response. Overall, p53 activation may trigger an adaptive immunity.

Several MDM2-p53 protein-protein interaction inhibitors are currently being evaluated in clinical trials [P20-06431; R17-0975] and showed both, on-target pharmacodynamic activity, as exemplified by growth differentiation factor-15 / GDF-15 (MIC-1) induction in plasma, as well as anti-tumour activity [R15-5326; R17-0998]. Indeed, objective responses and disease stabilizations in various tumour types, mainly MDM2-amplified, were observed in single agent trials as well as in combination trials.

Brigimadlin is a highly potent MDM2-p53 antagonist with demonstrated efficacy in preclinical mouse models of human cancer with intermittent dosing. Brigimadlin is orally available and showed high exposures in patients in Trial 1403-0001. The compound has a [redacted] which allows an intermittent dosing schedule that can mitigate serious adverse events.

1.4.2 Risks

Brigimadlin has been administered to more than 750 patients in ongoing clinical trials. Based on safety data from these patients and trial data from in-class competitors, the following potential treatment-induced side effects were identified, i.e. myelosuppression and gastrointestinal AEs:

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1) Myelosuppression

Myelosuppression, particularly thrombocytopenia and neutropenia, is the main toxicity associated with brigimadlin. Current data show that myelosuppression is dose dependent.

[redacted]

Several recommendations are in place to mitigate and manage the AEs related to myelosuppression, including the following key points:

- Safety laboratory assessments at appropriate intervals to monitor the severity of myelosuppression allow the investigators to properly treat the patients.
- General recommendations for the management of AEs related to myelosuppression are given in Section 4.2.1.
- Dose modification is allowed; see Section 4.1.4.2.

2) Gastrointestinal AEs

Data from the ongoing trials show that gastrointestinal AEs such as nausea, vomiting, and diarrhoea were common among treated patients [redacted]

General recommendations for the mitigation and management of treatment-induced gastrointestinal AEs are provided in Section 4.2.1.2.

Preliminary data suggest that brigimadlin has a moderate emetogenic risk level. Primary anti-emetic prophylaxis before Cycle 1 and on subsequent treatment is required. The choice of anti-emetic prophylaxis regimen is at the discretion of the investigator and should be based on local, national, international, and institutional guidelines. Recommendations are provided in Section 4.2.1.2.

3) [redacted]

[redacted]

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Other risks and measures to reduce risks are described below:

- As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected, or nerves may be damaged, inducing long-lasting abnormal sensations (paraesthesia), impaired sensation of touch and persistent pain. These risks will be addressed by careful safety monitoring and risk mitigation measures such as

  (a) compression
  (b) close clinical monitoring for AEs
  (c) selection of experienced sites and site staff
  (d) Safety recommendations provided in laboratory manual

- Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Patients treated with brigimadlin should be monitored for signs of liver injury according to guidelines specified in Section 5.2.6.1.4.

- Tumour biopsies may be taken for the purposes of the trial. There is an added risk for pain, swelling, and bleeding for those patients who will undergo tumour biopsies. For this reason, biopsies will only be performed when deemed safe by the investigator and if the platelet count is sufficient to allow for haemostasis. The biopsy results will provide valuable information and will assist clinical decisions for future patients. Hence, the benefit is assumed to outweigh the risks associated with the biopsy.

- Clinical imaging will expose the patient to a certain radiation burden. The imaging schedule is kept to the minimum in this trial. National regulations must be complied regarding the CT exposure for the purpose of this clinical trial.

- A data-monitoring committee (DMC) that is independent of the sponsor will review efficacy and safety analyses prepared by the sponsor. Further details about the planned analyses are given in Section 8.7. Details about the DMC are provided in Section 8.7 and will also be provided in a DMC charter.

- A steering committee (SC) will act as an advisory body. It will consist of independent experts, sponsor representatives, and investigator representatives. Details about the SC are provided in Section 8.7 and will also be provided in an SC charter.

1.4.3 Discussion

The nature of the target and the mechanism of action of brigimadlin are sufficiently understood.

In the context of the unmet medical need and the anticipated benefit of brigimadlin treatment, the benefit risk evaluation of the compound is favourable, based on the available preclinical and clinical information. The expected benefit outweighs the potential risks.

1.4.3.1 COVID-19 Benefit-risk assessment for brigimadlin

Patients in clinical trials with brigimadlin have advanced, late-stage cancer with limited treatment options. Given the life-threatening nature of the underlying disease, the approach

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recommended by professional oncology organizations (e.g. American Society of Clinical Oncology, European Society Medical Oncology) remains to treat patients with cancer as under normal circumstances. No consensus on recommendations exists regarding holding or delaying anti-cancer treatments in patients with or susceptible to Corona Virus Disease 2019 (COVID-19). Withdrawing treatment in a patient with cancer who may have few or no alternative treatment options requires a careful, individual evaluation.

To date, there is no evidence suggesting an association between an increased susceptibility to COVID-19 infection and MDM2-p53 inhibition by brigimadlin. Considering the limited data on immune activation and the role of inflammation as well as other underlying factors that may increase the severity and mortality of COVID-19 infection, there may be unknown risk factors associated with brigimadlin monotherapy. Information regarding relevant risk factors and recommendations from professional medical oncology organizations will be monitored.

There are no interactions expected between approved COVID-19 vaccines and the use of brigimadlin monotherapy. Patients treated with brigimadlin should be carefully monitored for myelosuppressive side effects before COVID-19 vaccination is started as guided by the vaccine labels. Interactions with COVID-19 therapeutics cannot be excluded, and restrictions should be considered (Section 4.2.2.1).

The inclusion of patients with cancer in trials with brigimadlin is evaluated on a single case basis, considering the totality of information related to each individual patient and the local COVID-19 situation. The sponsor, where required, will support the investigator in their decision finding.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will assess brigimadlin monotherapy in multiple cohorts of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type solid tumours. Each cohort will include patients with a specific cancer type:

- Cohorts 1 and 1-CN: biliary tract adenocarcinoma (cholangiocarcinoma, gallbladder cancer, and ampullary cancer)
- Cohort 2: pancreatic ductal adenocarcinoma
- Cohort 3: lung adenocarcinoma
- Cohort 4: urothelial bladder cancer

Additional cohorts of other MDM2 amplified, TP53 wild-type solid tumours may be added in future via protocol amendment.

Cohort 1 (biliary tract adenocarcinoma):

- Cohort 1 aims to assess the efficacy, safety, and tolerability of brigimadlin monotherapy in patients with locally advanced or metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma. Patient must have received appropriate prior standard of care therapy or, in the opinion of the investigator be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

- The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with objective response (OR).
- Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of duration of objective response (DOR), progression-free survival (PFS), and overall survival (OS) as well as the assessment of health-related quality of life as assessed by the EORTC QLQ-C30 and the EORTC QLQ-BIL21.
- The summary measure of the primary endpoint will include all treated patients who have received appropriate prior standard of care therapy, regardless of premature discontinuation of trial treatment, but will exclude the effects of any subsequent anti-cancer therapy started before disease progression.

Cohort 1-CN (biliary tract adenocarcinoma):

- Cohort 1-CN aims to assess the efficacy, safety, and tolerability of brigimadlin monotherapy in patients from mainland China with locally advanced or metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma. Patient must have received appropriate prior standard of care therapy or, in the opinion of the investigator be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.

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- The primary objective, secondary objectives, and summary measure of the primary endpoint are the same as for Cohort 1.

Cohort 2 (pancreatic ductal adenocarcinoma):

- Cohort 2 aims to assess the efficacy, safety, and tolerability of brigimadlin monotherapy in patients with locally advanced or metastatic, MDM2 amplified, TP53 wild-type pancreatic ductal adenocarcinoma. Patient must have received appropriate prior standard of care therapy.
- The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR.
- Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS.
- The summary measure of the primary endpoint will include all treated patients, regardless of premature discontinuation of trial treatment, but will exclude the effects of any subsequent anti-cancer therapy started before disease progression.

Cohort 3 (lung adenocarcinoma):

- Cohort 3 aims to assess the efficacy, safety, and tolerability of brigimadlin monotherapy in patients with locally advanced or metastatic, MDM2 amplified, TP53 wild-type lung adenocarcinoma. Patient must have received appropriate prior standard of care therapy.
- The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR.
- Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS.
- The summary measure of the primary endpoint will include all treated patients, regardless of premature discontinuation of trial treatment, but will exclude the effects of any subsequent anti-cancer therapy started before disease progression.

Cohort 4 (urothelial bladder cancer):

- Cohort 4 aims to assess the efficacy, safety, and tolerability of brigimadlin monotherapy in patients with locally advanced or metastatic, MDM2 amplified, TP53 wild-type urothelial bladder cancer. Patient must have received appropriate prior standard of care therapy.
- The primary objective is to evaluate the efficacy of brigimadlin by the proportion of patients with OR.
- Secondary objectives are to evaluate the efficacy of brigimadlin by median estimate of DOR, PFS, and OS.
- The summary measure of the primary endpoint will include all treated patients, regardless of premature discontinuation of trial treatment, but will exclude the effects of any subsequent anti-cancer therapy started before disease progression.

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2.1.2 Primary endpoint(s)

The primary endpoint of the trial is objective response (OR) based on central independent review. OR is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 from the date of treatment start until the earliest date of disease progression, death, or last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent.

2.1.3 Secondary endpoint(s)

Secondary endpoints of the trial are:

- Duration of objective response (DOR) based on central independent review. DOR is defined as the time from first documented confirmed objective response (OR) until the earliest date of disease progression or death among patients with confirmed objective response.
- Progression-free survival (PFS) based on central independent review. PFS is defined as the time from treatment start until the earliest date of tumour progression according to RECIST version 1.1 or death from any cause, whichever occurs first.
- Overall survival (OS), defined as the time from treatment start until death from any cause.
- Disease control (DC) based on central independent review. DC is defined as a best overall response of CR, PR, or stable disease (SD) where best overall response is defined according to RECIST version 1.1.
- Occurrence of treatment-emergent adverse events (AEs) during the on-treatment period.
- Occurrence of treatment-emergent AEs leading to trial drug discontinuation during the on-treatment period.
- The following endpoints reflecting patient-reported outcomes (PRO) will be assessed with the following PRO measures (PROMs), for Cohorts 1 and 1-CN only:
    - Change from baseline in EORTC QLQ-C30 physical functioning domain score
    - Change from baseline in EORTC QLQ-C30 fatigue domain score
    - Change from baseline in EORTC QLQ-C30 role functioning domain score
    - Change from baseline in EORTC QLQ-BIL21 tiredness domain score

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives of the trial are to explore further measures of efficacy and PRO as well as the assessment of PK and biomarkers.

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2.2.2 Further endpoints

Further endpoints of the trial are:

- Progression-free survival based on investigator assessment. PFS is defined as the time from treatment start until the earliest date of tumour progression according to RECIST version 1.1 or death from any cause, whichever occurs first.
- Objective response based on investigator assessment. OR is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1.
- Duration of objective response based on investigator assessment. DOR is defined as the time from first documented confirmed OR until the earliest date of disease progression or death among patients with objective response.
- Disease control based on investigator assessment. DC is defined as a best overall response of CR, PR, or SD where best overall response is according to RECIST version 1.1.
- Time to treatment failure (TTF) is defined as the time from first treatment administration until discontinuation of treatment for any reason, including but not limited to disease progression, treatment toxicity, and death.
- Pharmacokinetics (PK) of brigimadlin at Cycle 1: maximum plasma concentration (C_{max}) and $AUC_{0\text{-}tz}$.

[redacted]

- Further endpoints reflecting PRO will be assessed with the following PRO measures (PROMs):
    - Changes in EORTC QLQ-C30 and EORTC IL46 (item 168) scores
    - Changes in PGIS and PGIC scores
    - Cohorts 1 and 1-CN only: Changes in EORTC QLQ-BIL21 scores
    - Cohort 2 only: Changes in EORTC QLQ-PAN26 scores
    - Cohort 3 only: Changes in NSCLC-SAQ scores

More details and additional further endpoints may be defined in the trial statistical analysis plan (TSAP).

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

The overall trial design is an open-label, single-arm, seamless Phase IIa/IIb trial as shown in Figure 1.

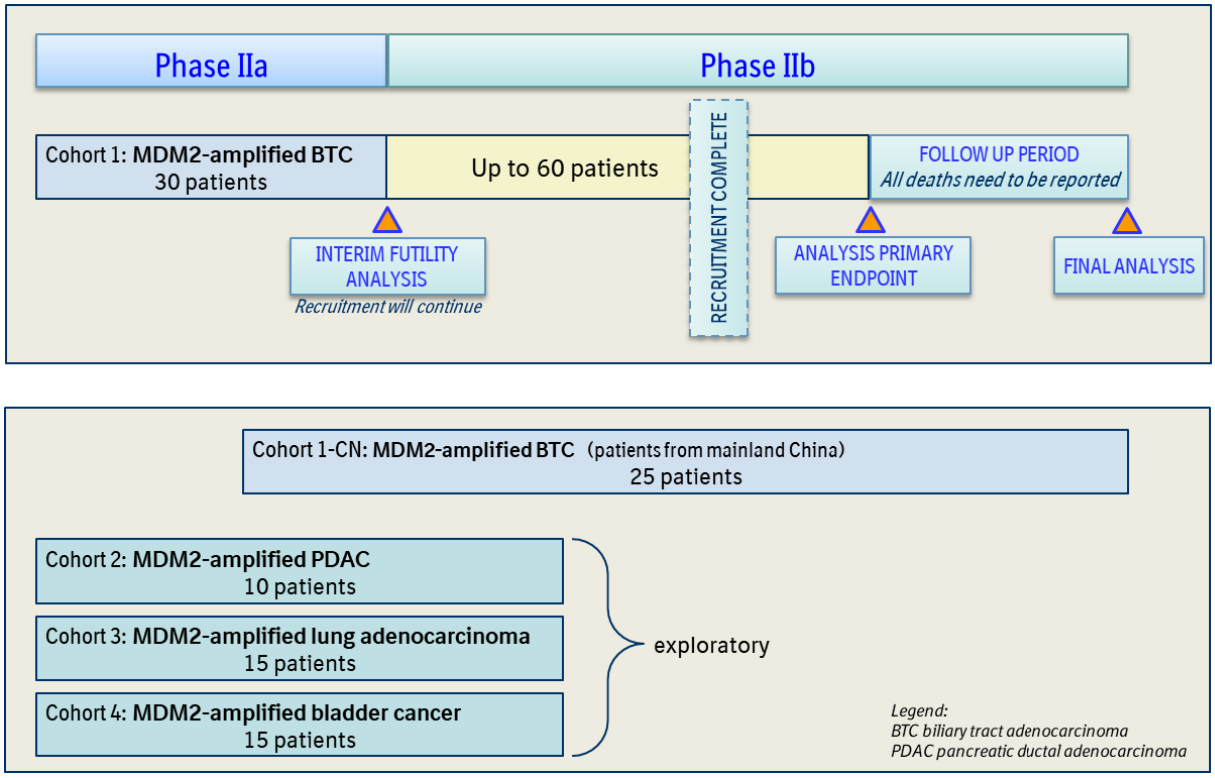


Figure 1 Trial design for Phase II trial 1403-0011

The Phase IIa part has cohorts with 4 cancer types: Cohort 1 and Cohort 1-CN are for patients with biliary tract adenocarcinoma. Patients recruited in mainland China will be allocated to Cohort 1-CN, and those from rest of the world will be allocated to Cohort 1. Cohort 2 is for patients with pancreatic ductal adenocarcinoma, Cohort 3 is for patients with lung adenocarcinoma, and Cohort 4 is for patients with urothelial bladder cancer. Cohorts for other specific tumour indications will be added via protocol amendment based on evolving Phase Ib data.

There is no control arm. All patients receive 45 mg brigimadlin, once every 3 weeks (D1q3w).

For Cohort 1, the primary endpoint OR will be assessed at 2 timepoints: (1) at the interim futility analysis when the first 30 treated patients have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier; and (2) at the primary analysis when all treated patients (approximately 90 patients) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier.

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If Cohort 1 passes the futility boundary, then the cohort will enter the Phase IIb part. Enrolment of patients will continue whilst this analysis is performed. The total sample size for Cohort 1 will be approximately 90 patients.

Patient enrolment in Cohort 1-CN will open and continue independently of the conduct and analysis of cohort 1. The total sample size for Cohort 1-CN will be approximately 25 patients.

The planned sample size for Cohorts 2, 3, 4 is approximately 10, 15, and 15 patients respectively. A futility analysis will be performed to confirm the efficacy signal before deciding on the next steps.

The total number of patients for the entire trial is approximately 155 patients.

Patients will continue to receive treatment with brigimadlin until disease progression (PD) according to RECIST or until another reason requiring termination of treatment (see Section 3.3.4).

Treatment beyond progression will be allowed if the investigator judges that this would provide continued clinical benefit to the patient (see Section 6.2.4).

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

An open-label, single-arm, seamless Phase IIa/IIb design was considered most appropriate to assess the efficacy, safety, and tolerability of brigimadlin as systemic therapy for locally advanced / metastatic biliary tract adenocarcinoma, locally advanced / metastatic pancreatic ductal adenocarcinoma, or other solid tumours. The seamless design was chosen to bring new treatments faster to a patient population with a high unmet need.

The trial will include different locally advanced / metastatic cancer types not suitable for targeted treatment and/or standard of care. Treatment options for these patients are limited and often consist of several, subsequent chemotherapies that are not suitable for many patients and show minimal efficacy. Furthermore, so far, no MDM2-targeting therapy has been approved in any indication.

- Biliary tract adenocarcinoma (Cohorts 1 and 1-CN): gemcitabine + cisplatin is standard of care in 1st line treatment, addition of a checkpoint inhibitor might be possible. FOLFOX has a category 2A recommendation by NCCN for 2nd line treatment based on the ABC-06 trial (FOLFOX vs best supportive care) showing a median OS of 6.2 vs 5.3 months, and an ORR of 5% [R22-0948]. Recently, the NIFTY-trial (Phase IIb trial comparing liposomal irinotecan + 5-FU/LV vs FU/LV) reported a median OS of 8.6 vs 5.5 months with an ORR of 14.8% vs 5.8% [R22-1705].
- Pancreatic ductal adenocarcinoma (Cohort 2): FOLFIRINOX or nab-paclitaxel + gemcitabine are standard of care in 1st line treatment. The benefit of 2nd line chemotherapy is modest and not many patients are eligible. The NAPOLI-regimen (nanoliposomal irinotecan at 80 mg/m² with fluorouracil and folinic acid every 2 weeks) after gemcitabine-based 1st line treatment showed a median overall survival (OS) of ~6 months and an ORR of 16% [R21-0224]; the limited available data for gemcitabine + nab-paclitaxel after FOLFIRINOX indicate a similar outcome

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[R22-1698]. Gemcitabine or fluoropyrimidine-based regimens + oxaliplatin resulted in a median PFS of 3.1 months, a median OS of 5-7 months, and an ORR <5% [R22-1697].

- Currently, patients with advanced/metastatic lung adenocarcinoma receive, depending on their molecular profile targeted therapy such as EGFR-TKIs, checkpoint inhibitors +/- chemotherapy, and chemotherapy (platinum-doublet, but also in combination with anti-angiogenic substances, or as monotherapy). However, eventually patients run out of treatment options (≥ 3rd line, depending on alteration/s and prior therapies). Monotherapy with chemotherapy (e.g. docetaxel) in 2nd or later lines results in mOS of around 9 months, a PFS of 3-4 months, and ORR around 13% [R16-5828, R14-3261, R16-1875].
- NCCN explicitly recommends participation in clinical trials of new agents for patients with bladder cancer after first-line progression. Therapy options in second-line chemotherapy compromise (depending on first-line treatment and patient's condition) checkpoint inhibitors, chemotherapy, and enfortumab-vedontin. Median overall survival in second-line is 5-9 months, with enfortumab-vedontin up to 13 months, median PFS 4-6 months, and ORR of around 18%, with enfortumab 41% [R22-4068, R22-4066].

The trial is designed to allow the addition of new cohorts via amendment of the clinical trial protocol as efficacy data emerges from the ongoing Phase I clinical trials.

3.3 SELECTION OF TRIAL POPULATION

The trial will be conducted in about 75 sites in multiple countries and regions. Additional sites might be added as needed to fulfil the planned enrolment. If site(s) are unable to recruit patients, additional sites may be opened, and non-enrolling sites may be closed. The total number of planned patients in this trial is 155 patients (90 patients in Cohort 1, 25 patients in Cohort 1-CN, 10 patients in Cohort 2, and 15 patients in Cohorts 3 and 4).

Boehringer Ingelheim is committed to ensuring that a representative patient population is recruited in its clinical trials. Regulatory authorities and/or Boehringer Ingelheim in some countries may impose certain population target/s such as gender, race, ethnicity, and age for certain clinical trials. Principal Investigators and sites will be notified of the population target/s for their specific country. Upon this notification, or at some point thereafter, it may be requested to provide tactics and strategies to achieve those target/s and progress against those target/s over the course of the clinical trial. To achieve the required population target/s, sites may be asked to focus their efforts on the recruitment of a certain sub-set of patients. This may even require Boehringer Ingelheim to stop patient recruitment at certain sites and to continue recruitment at other sites. This approach enables treatments to be evaluated in the patients who will ultimately use them.

The trial will aim to recruit a balance of patients from multiple regions, but recruitment will initially be unrestricted. If an imbalance in recruitment starts to occur, a cap on recruitment in specific countries and/or regions may be introduced to ensure a balance will be achieved.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional

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patients for this trial. Patients already in screening at this time will be allowed to continue and enter the trial if eligible.

Assessments may be repeated within the screening period if patients do not initially meet the inclusion / exclusion criteria. Eligibility must always be assessed using the latest results available. Re-screening of patients who have previously failed screening will be permitted once; a new patient number will be assigned to those patients.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been entered in error (= did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

The trial will include patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type solid tumours.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Diagnosis of a solid tumour which meets the criteria for an open trial cohort:
    - Cohorts 1 and 1-CN (biliary tract adenocarcinoma): Locally advanced or metastatic biliary tract adenocarcinoma (intra- and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer). Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards; or (in the opinion of the investigator) patients are unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy.
    - Cohort 2 (pancreatic ductal adenocarcinoma): Locally advanced or metastatic pancreatic ductal adenocarcinoma. Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.
    - Cohort 3 (lung adenocarcinoma): Locally advanced or metastatic lung adenocarcinoma. Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.
    - Cohort 4 (urothelial bladder cancer): Locally advanced or metastatic urothelial bladder cancer. Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.

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2. Written pathology report / molecular profiling report indicating MDM2 amplification*, and TP53 wild-type status. This must have been confirmed with a tissue-based test. A test with liquid biopsy is not accepted.
   * The MDM2 copy number must be ≥8. An exception is when the molecular pathology test has been performed by a laboratory designated by the sponsor for development of the companion diagnostic test (see section 5.4.2.1), in which case the copy number information is not required.
3. Archival tissue (formalin fixed paraffin embedded [FFPE] tumour blocks or slides) must be provided for retrospective confirmation of MDM2 amplification and TP53 status. See Section 5.4.2.1 for details and an exception.
4. Presence of at least 1 measurable target lesion according to RECIST version 1.1.
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
6. Patient must be willing to donate mandatory blood samples for the pharmacokinetics, pharmacodynamics, and biomarker analyses, as specified in the Flowchart.
7. Adequate organ function, defined as meeting all criteria in Table 1.
8. All toxicities related to previous anti-cancer therapies have resolved to ≤CTCAE Grade 1 prior to trial treatment administration (except for alopecia and amenorrhea / menstrual disorders which can be of any grade and peripheral neuropathy which must be ≤CTCAE Grade 2).
9. Life expectancy ≥3 months at the start of treatment in the opinion of the investigator.
10. Provision of signed and dated, written informed consent form (ICF) in accordance with ICH-GCP and local legislation prior to any trial-specific procedures, sampling, or analyses.
11. Male or female patients ≥18 years old at the time of signature of the ICF. Women of childbearing potential (WOCBP; for a definition see Section 4.2.2.3) and men able to father a child must be ready and able to use 2 medically acceptable methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation, and until 6 months and 12 days after last dose for women and 102 days after last dose for men. A list of contraception methods meeting these criteria is provided in the patient information.

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Table 1 Screening reference laboratory values

System	Laboratory Value
Haematological	
Absolute neutrophil count	≥1.5×10^9/L (or ≥1.5×10^3/μL or ≥1500/mm^3)
Platelets	≥100×10^9/L (or ≥100×10^3/μL or ≥100×10^3/mm^3)
Haemoglobin	≥8.0 g/dL or ≥5.0 mmol/L or ≥80 g/L
Hepatic	
Total bilirubin	≤1.5×upper limit of normal (ULN), (patients with Gilbert's syndrome, total bilirubin must be ≤3×ULN)
AST and ALT	≤2.5×ULN OR ≤5×ULN for patients with liver metastases
Renal	
Estimated glomerular filtration rate (eGFR)	>45 mL/min (calculated using Chronic Kidney Disease Epidemiology [CKD-EPI] formula)
Coagulation	
International Normalised Ratio (INR) or Prothrombin Time (PT) AND Activated Partial Thromboplastin Time (aPTT)	≤1.5×institutional ULN unless on a stable dose of an anticoagulant with no unexplained elevation of INR Patients taking low dose warfarin must have their INR followed closely and according to institutional guidelines

3.3.3 Exclusion criteria

1. Previous administration of brigimadlin or any other MDM2-p53 or MDMX (MDM4)-p53 antagonist.
2. Active bleeding, significant risk of haemorrhage (e.g. previous severe gastrointestinal bleeding, previous haemorrhagic stroke at any time), or current bleeding disorder (e.g. haemophilia, von Willebrand disease).
3. Major surgery (major according to the investigator's assessment) performed within 4 weeks prior to start of trial treatment or planned within 6 months after screening (e.g. hip replacement).
4. Clinically significant previous or concomitant malignancies in the opinion of the investigator affecting the efficacy and/or outcome of the trial.
5. Patients who must or intend to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
6. Currently enrolled in another investigational device or drug trial.
7. Any history of, or concomitant condition that, in the opinion of the investigator, would compromise the patient's ability to comply with the trial or interfere with the evaluation of the safety and efficacy of the trial drug.
8. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).

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9. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Female patients who do not agree to the interruption of breastfeeding from the start of trial treatment until 6 months and 12 days after last dose of trial treatment.
10. Patients with known history of human immunodeficiency virus (HIV) infection who meet 1 or more of the following criteria:
    - CD4+ count <350 cells/µL
    - Viral load >400 copies/mL (local laboratory assessment)
    - Not receiving antiretroviral therapy
    - Receiving established antiretroviral therapy for <4 weeks prior to the start of trial treatment
    - History of AIDS-defining opportunistic infections within 12 months prior to start of trial treatment

    Patients with a history of HIV who do not meet any of the criteria above are eligible to participate but the patient must be under the care of a HIV/Infectious Diseases specialist or a HIV/Infectious Diseases specialist must be consulted prior to inclusion.
11. Patients with a history of HCV infection who meet 1 or more of the following criteria:
    - Currently receiving curative antiviral treatment
    - Not yet achieved sustained viral response (SVR)
    - HCV viral load is above the limit of quantification (HCV RNA positive)
12. Patients with chronic HBV infection with active disease who meet the criteria for anti-HBV therapy (according to local / institutional standard) and who have not been treated with suppressive antiviral therapy prior to initiation of trial treatment.
13. Any history or presence of uncontrolled gastrointestinal disorders that could affect the intake and/or absorption of the trial drug (e.g. nausea, vomiting, Crohn's disease, ulcerative colitis, chronic diarrhoea, malabsorption) in the opinion of the investigator.
14. Known hypersensitivity to brigimadlin or any of its excipients.
15. Active severe infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at treatment start in this trial. Cholangitis being treated for at least 1 week with antibiotics and well controlled is allowed.
16. History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥III or IV, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator. Myocardial infarction, stroke or pulmonary embolism within 6 months prior to the start of trial treatment.
17. Patients with uncontrolled ascites related to portal hypertension and/or active, uncontrolled cholangitis.
18. Receiving treatment for brain metastases or leptomeningeal disease (LMD) which may interfere with safety and/or efficacy endpoint assessment [1].

[1] Please check carefully if any of the treatments being taken by the patient potentially lower the seizure threshold or have cytochrome P450 interaction. Such cases should be discussed between the sponsor and investigator to agree on exclusion of patients treated with specific anticonvulsants with a specific threshold.

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19. Any of the following cardiac criteria:
    - Mean resting corrected QT interval (QTcF) >470 msec
    - Any clinically important abnormalities (as assessed by the investigator) in rhythm, conduction, or morphology of resting ECGs, e.g. complete left bundle branch block, third degree heart block
    - Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age.
    - Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of trial drug can be accepted provided that there is clinical evidence that the patient's cardiac disease has not significantly worsened since this measurement in the opinion of the Investigator or of the treating physician or both.

20. Patients who cannot swallow pills.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

However, if the patients agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

The patient should attend all remaining visits as outlined in the reduced schedule Flowchart, which no longer includes follow-up for disease progression. Prior to Global amendment 5, this included the follow-up for disease progression assessments if a patient discontinued treatment prior to documented objective disease progression and did not start subsequent anti-cancer treatment. Should the patient not agree, at least phone contacts should occur at the scheduled visit time points, should that not be acceptable, a phone contact once a year or at the end of the planned observation period should occur to collect the most relevant

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information: vital status, outcome events, adverse events, or last contact date in case of lost to follow-up.

An individual patient will discontinue treatment if:

The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.

- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons such as surgery, adverse events, or other diseases. This includes specified adverse events requiring discontinuation as described in Section 4.1.4.2.

The patient has radiological documentation of progressive disease by investigator assessment on the current treatment (see Section 5.1), unless the investigator documents that the patient will continue treatment beyond progression due to continued clinical benefit (see Section 6.2.4).

The patient becomes pregnant during the trial. Treatment with brigimadlin must then be stopped immediately. The patient will be followed up until delivery or termination of pregnancy.

In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4.

As of Global Amendment 5, the sponsor may remove patients on treatment with brigimadlin from the trial if the patient has access to brigimadlin via an alternative clinical trial, marketed product, an expanded access program, named patient use program, compassionate use protocol or other means based on local regulation. The cost of any ongoing supply of brigimadlin will be incurred by the sponsor until disease progression or any other reason for treatment discontinuation occurs. If a patient is removed from the trial treatment in these circumstances, an end of treatment and follow-up visit will be performed to ensure all adverse events are followed up and then the patient will be considered to have completed the trial. If a patient receives brigimadlin in another clinical trial, safety follow-up in this trial will end, and safety follow-up will continue uninterrupted in the new trial. Follow-up for overall survival may continue if required by the sponsor (see Section 6.2).

If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flowchart and Section 6.2.3.

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3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. All efficacy analyses (see Section 7) are complete and all patients have either ended trial treatment or are eligible to receive brigimadlin under the conditions listed in Section 3.3.4.1.

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

The trial investigates brigimadlin monotherapy.

Substance:	Brigimadlin
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Single dose on Day 1 every 21 days (D1q3w) Up to 2 dose reductions are permitted, unless an exemption is granted (see Section 4.1.4)
Route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

In the Phase I dose escalation Trial 1403-0001, brigimadlin was assessed [redacted] dosing schedule (Arm A). [redacted]

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4.1.3 Method of assigning patients to treatment groups

There will be no randomisation in this trial, as it is a single-arm open-label trial. After the assessment of all in- and exclusion criteria, the appropriate medication number for each eligible patient will be documented in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

Patients will take a single oral dose of brigimadlin on Day 1 every 21 days (D1q3w) until the development of progressive disease (unless treatment beyond progression has been agreed, see Section 6.2.4), or until other criteria for stopping medication are met. Patients will be monitored closely for adverse events and the dose of brigimadlin may be reduced if needed, according to the instructions provided in Section 4.1.4.2)

4.1.4.1 Administration of trial medication

[redacted] Brigimadlin will be provided in bottles with child-resistant screw cap closure. The packaging will include 1 tablet per bottle. The tablet should be stored in the container provided and handled according to the labelled storage instructions and shelf life. Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The different tablet strengths should not be combined in the same bottle at any time. Brigimadlin will be stored at each investigational site.

Brigimadlin should only be administered if all the following criteria are met:

- Absolute neutrophil count is $\geq 1.5 \times 10^9$/L
- Platelet count is $\geq 100 \times 10^9$/L (In case of platelet transfusion after the last drug administration, this criterion must be met in a measurement taken at least 72 hours after the last platelet transfusion)
- Any related SAE/AE which required a dose delay (see Section 4.1.4.2) has recovered to ≤CTCAE Grade 1 or to baseline value (except for haemoglobin, where the patient must recover to ≥8.0 g/dL or ≥4.9 mmol/L or ≥80 g/L).

[redacted]

The medication will be administered in the clinic, as a single oral dose, with about 240 mL (approximately 8 U.S. ounces) water, in the standing or sitting position, under supervision of the investigating physician or an authorised designee on Day 1 of each cycle. In Cycle 1, brigimadlin should be taken in the morning, taking into account the PK sampling.

[redacted]

Patients with emesis should not take a replacement dose. Any occurrence of vomiting within 12 hours of brigimadlin administration should be documented in the medical record and the eCRF.

Pre-dose laboratory PK samples will be collected ≤72 hours prior to receiving each single dose of brigimadlin.

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Dose escalation is not allowed; all patients will remain on the dose allocated to them at the start of the trial, unless dose reduction is required (see Section 4.1.4.2).

4.1.4.2 Guidance for dose delays and dose reductions for brigimadlin

Adverse events requiring discontinuation

Treatment will be permanently discontinued if the following events related to brigimadlin occur:

- CTCAE Grade 4 AEs with the exception of myelosuppressive AEs of CTCAE Grade 4 (e.g. neutropenia, thrombocytopenia, anaemia) for which targeted treatment options and blood transfusion are available (Section 4.2.1).
- Adverse events which cause a dose delay and do not recover within the allowed time window, as described in the sections below.
- Patient requires more than 2 dose reductions, unless the investigator deems treatment continuation beneficial, and a 3rd dose reduction is agreed between the investigator and the sponsor.

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Guidance for dose delays of brigimadlin due to low platelet and/or neutrophil count

Platelet and neutrophil count are assessed on the **planned** Day 1 of (or within 72 hours prior to) each treatment cycle. **Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle.** Treatment pauses due to changes in platelet count and/or neutrophil count must [redacted]

[redacted]

Guidance for dose delays of brigimadlin due to other adverse events

- For an individual patient, delays to dosing will be based on observed adverse events, safety laboratory test results prior to treatment administration, and clinical assessments during the previous cycle and on the planned day of treatment.
- Patients will be assessed on the planned Day 1 of the treatment cycle. **Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle.** If dosing is delayed, then the Day 1 visit and assessments are also delayed.
- If an AE of CTCAE Grade ≥3 is considered to be related to brigimadlin, treatment should be paused until the patient has recovered from the drug-related toxicity to Grade ≤1 or baseline (except for haemoglobin, where the patient must recover to ≥ 8.0 g/dL or ≥ 4.9 mmol/L or ≥80 g/L). Baseline is defined as the CTCAE grade at the start of treatment. If treatment-related CTCAE Grade 2 AEs persist for ≥7 days

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despite treatment or are poorly tolerated by the patient, the investigator may choose to pause treatment to allow recovery.

Patients should be assessed weekly until recovered.

[redacted]

- Dosing may be delayed to allow for recovery of an adverse event unrelated to brigimadlin. This is at the discretion of the investigator. No dose reduction should occur.
- Dosing may be delayed for up to 3 days for other non-safety related reasons (e.g. administrative). No dose reduction should occur.

Brigimadlin dose reduction guidelines

- Any dose reduction will be permanent (i.e. dose re-escalation is NOT allowed).
- Up to 2 dose reductions of brigimadlin are allowed. For patients who require more than 2 dose reductions, brigimadlin should be permanently discontinued unless the investigator deems treatment continuation beneficial with or without dose reduction. This must be agreed with the sponsor. [redacted]

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

There will be no blinding in this trial, as it is a single-arm open-label trial (see justification in Section 3.2).

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4.1.5.2 Unblinding and breaking the code

Not applicable for this trial.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). The label will be prepared according to EU Regulation No. 536/2014, Annex 6, Section D.8. "Investigator Name", was omitted from the label and it is covered by Trial Identification Card (TIC). "Visit number" is not relevant for the label because the product will remain at the clinical site. The Visit number (cycle number) is managed in the IRT and additionally the Med. No on the label allows correct traceability and documentation of the corresponding cycle. Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. The address and telephone number of the main contact was omitted from the label because a Trial Identification Card (TIC), which includes the main contact and telephone number, will be issued to each trial participant.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA; as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this clinical trial protocol. They must not be forwarded to other investigators or clinics.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Rescue medications to reverse the actions of brigimadlin are not available. Therefore, potential side effects must be treated symptomatically or as specifically noted below. All concomitant medications must be used in accordance with the package insert / summary of product characteristics.

4.2.1.1 Prevention and treatment of haematological adverse events



Colony-stimulating factors (CSFs) must be considered in patients with fever and neutropenia who are at high risk for infection-associated complications, or who have prognostic factors that are predictive of poor clinical outcomes. High-risk features include expected or observed prolonged (>7 days) and profound ($<0.1\times10^9$/L) neutropenia, age older than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis

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syndrome), invasive fungal infection, or being hospitalised at the time of the development of fever (guidance based on ASCO guideline update 2015).

Erythropoietin-stimulating agents (ESAs) can be offered to patients with treatment-associated anaemia. Red blood cell transfusion may be an option, depending on the severity of the anaemia or clinical circumstances.

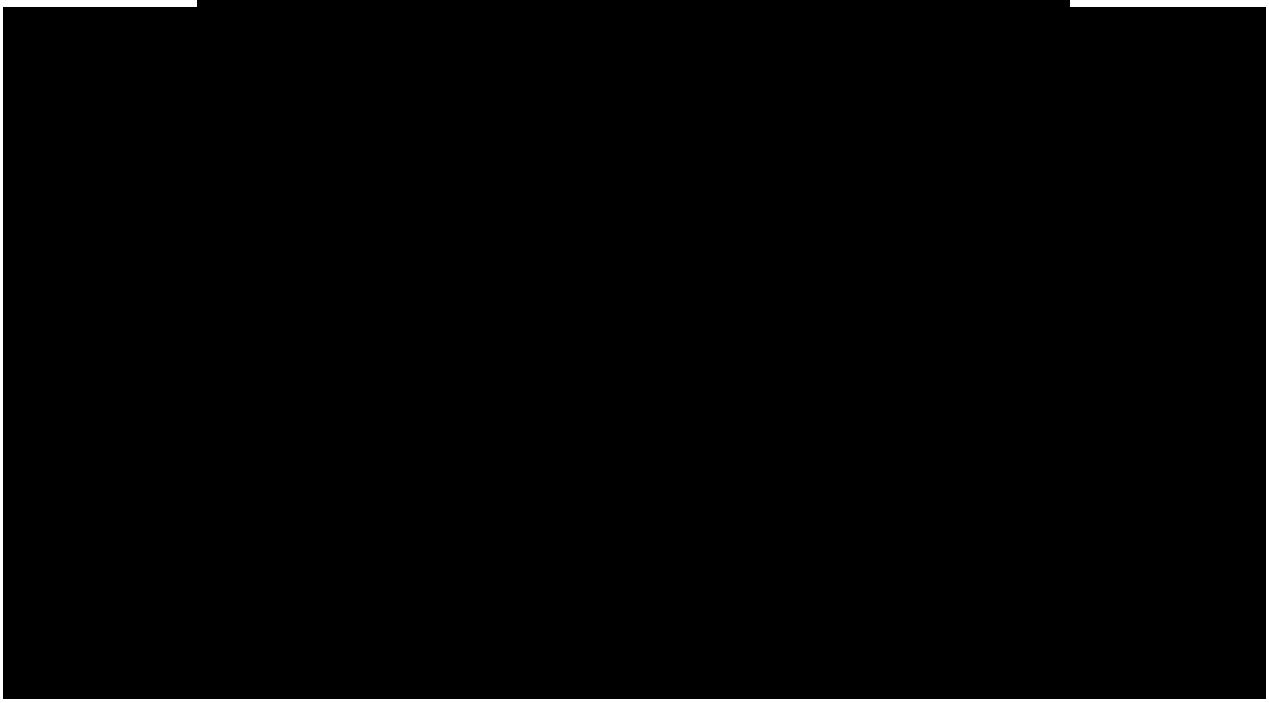
Platelet transfusion must be considered in patients with a platelet count $<10\times10^9$/L. Platelet transfusion when the platelet count is $>10\times10^9$/L may be appropriate in patients with active localised bleeding (guidance based on ASCO guideline update 2017).

For patients with thrombocytopenia of CTCAE Grade 3 or 4 who are under treatment with anticoagulants, weekly controls of the blood counts and coagulation parameters should be performed.

There must be at least 1 week between a patient's last transfusion and their screening laboratory assessment. Exceptions to this will be considered by the sponsor on a case-by-case basis.

4.2.1.2 Prevention and treatment of gastrointestinal adverse events

Preliminary data suggest that brigimadlin has a moderate emetogenic risk level. Primary anti-emetic prophylaxis before Cycle 1 and on subsequent treatment days is required. The choice of anti-emetic regimen is at the discretion of the investigator and should be based on local, national, international, and institutional guidelines. Restrictions must also be taken into consideration.



In addition, anti-diarrheal agents are recommended in accordance with international and local guidelines.

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4.2.1.3 Treatment of other adverse events or concomitant medical conditions

- Treatment with corticosteroids is permitted when clinically indicated.
- Bisphosphonates for patients with lytic bone metastases.
- After trial enrolment, palliative radiotherapy may be given for bone pain or for other reasons (e.g. bronchial obstruction, skin lesions), provided that the total dose delivered is in a palliative range according to institutional standards. The irradiated area cannot be used for further tumour response assessment. During palliative radiotherapy, trial treatment should be delayed and may be resumed once the patient has recovered from any radiation associated toxicity. If medication is delayed for more than 14 days, the decision to continue will be made by the sponsor in agreement with the investigator.
- Local therapy (radiotherapy, surgery, ablation) of target lesions should be avoided wherever possible. If local therapy is given, the treated area cannot be used for further tumor response assessment. Further treatment must be agreed between the sponsor and the investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Concomitant therapy, with reasons for the treatment, must be recorded in the eCRF during the screening and treatment periods, starting at the date of signature of informed consent and ending after the residual effect period (REP). After the REP, only concomitant therapy indicated for treatment of a related AE has to be reported. If a new anti-cancer treatment is started, it will be documented in the eCRF, on a separate page of follow-up therapy, different from the concomitant therapy pages.

No experimental anti-cancer treatment and/or standard chemotherapy, immunotherapy, hormone treatment, or radiotherapy (other than described in Section 4.2.1.3) is allowed concomitantly with the administration of trial treatment. The use of megestrol acetate to improve appetite and to increase weight in cancer-associated anorexia is allowed.

[redacted]

- Brigimadlin reduces CYP2B6 mRNA and activity *in vitro* and may therefore increase the exposure of drugs that are CYP2B6 substrates. Therefore, concomitant administration of any known CYP2B6 substrates is not allowed. For a list of CYP2B6 substrates please refer to Table 8.
- Brigimadlin is an inhibitor of P-gp and BCRP in *in vitro* studies with IC_{50} values of 8.6 µM and 7.2 µM, respectively. Assessment of the DDI likelihood according to FDA guidelines suggest that the inhibition of intestinal P-gp and BCRP would likely occur at brigimadlin dose levels exceeding 12 mg and 10 mg, respectively. P-gp or BCRP substrates with a narrow therapeutic window or index (NTI) are prohibited

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during the trial. P-gp or BCRP substrates without a narrow therapeutic index may be used with caution or should be replaced with alternatives wherever possible. For a list of prohibited P-gp substrates see Table 8.

- Based on clinical data brigimadlin can be considered a weak, transient CYP3A4 inducer at the clinically relevant dose and dosing schedule (45 mg q3w). Coadministration of brigimadlin with CYP3A4 sensitive substrates, for which minimal concentration changes may lead to therapeutic failures of the substrate, should be avoided. If coadministration cannot be avoided, follow recommendations for CYP3A4 inducers provided in their approved product label.
- Brigimadlin is a potential inducer of CYP1A2, based on in vitro studies. Drugs that are known CYP1A2 substrates may have reduced exposure and therefore reduced efficacy when given together with brigimadlin. Alternatives with less potential for CYP1A2-based interactions or concomitant drug dose adjustment should be considered if possible.
- Brigimadlin is in part metabolised by CYP3A4 according to *in vitro* hepatocyte data. Thus, the exposure of brigimadlin might be influenced by concomitant medications that are inducers and inhibitors of CYP3A4. Concomitant medications that are strong inhibitors or inducers of CYP3A4 are prohibited, starting 7 days prior to start of brigimadlin treatment. See Table 8 for a list of examples of prohibited strong CYP3A4 inhibitors and CYP3A inducers. Other inhibitors or inducers of CYP3A4 should be administered with care and the patient should be more closely monitored.
- Patients may continue to receive anti-coagulants which are either P-gp substrates (edoxaban, at doses <60 mg), or substrates of CYP3A4 and P-gp/BRCP (rivaroxaban, apixaban) whilst participating in the trial. Close monitoring is recommended, particularly on days when brigimadlin is administered, and an interval of approximately 8 hours between brigimadlin intake and intake of anti-coagulant can be considered. Use of edoxaban at doses ≥60 mg, dabigatran and betrixaban is prohibited.
- Brigimadlin reduces CYP2C9 mRNA and CYP2C19 enzyme activity in vitro. Drugs that are known CYP2C9 and CYP2C19 substrates may have increased exposure and therefore increased risk for side effects when given together with brigimadlin. Specifically, sensitive substrates and substrates with narrow therapeutic window or index [redacted]

[redacted] Other treatments are allowed taking into consideration the restrictions detailed in this section and in Section 1.4.2.

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In addition to the restrictions detailed above, the following concomitant medications should be handled as follows:

- Live attenuated vaccines are prohibited during the trial and until 30 days after the last dose of brigimadlin.
- Concomitant medications known to prolong the QT interval should be avoided where medically possible, and should be used with care if not avoidable.
- Herbal preparations/medications are allowed throughout the trial at the discretion of the investigator. Potential interactions described above should be taken into consideration.

COVID-19 vaccine

It is recommended that the treating physician consider vaccination against SARS-CoV-2 using the vaccines that have been authorised by the regulatory agencies for the patients participating in these BI clinical trials, provided that a benefit-risk assessment by the treating physician is favourable. Given the mode of action of brigimadlin, it is not anticipated that it would adversely interfere with the response to the vaccines.

This recommendation is consistent with the recommendation by professional oncology organizations (e.g. ASCO, ESMO and SITC).

4.2.2.2 Restrictions on diet and lifestyle

Patients should be instructed to avoid consumption of Seville oranges and grapefruit and their products on days when brigimadlin is administered, [redacted]

4.2.2.3 Contraception requirements

A woman is considered of child-bearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

WOCBP and men able to father a child must use two medically approved methods of birth control throughout the trial. They must use one barrier method, i.e. condom or occlusive cap with spermicide, and one highly effective non-barrier method including oral, injected or implanted hormonal contraceptives, intrauterine device or system. These requirements also apply regardless of whether the male is vasectomised.

Male patients:

Men whose partner is a WOCBP must use a condom (regardless of whether the male is vasectomised) and their female partner must use a highly effective form of contraception, during the trial and until 102 days after the last dose of trial medication (calculated as the period of relevant systemic exposure [5 half-lives plus 90 days]).

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Female patients:

WOCBP must use two medically approved methods of birth control, including a highly effective method of birth control (as outlined in the patient information) per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation, and until 6 months and 12 days after the last dose of trial medication (calculated as the period of relevant systemic exposure [5 half-lives plus 6 months]).

Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Alternatively, patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to trial drug; and withdrawal are not acceptable.

The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives and experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.

Additionally, ovum or sperm donation is not permitted during the periods of contraception.

4.3 TREATMENT COMPLIANCE

Brigimadlin should only be used as directed in this clinical trial protocol. Brigimadlin will be administered orally and only if considered safe by the investigator.

Brigimadlin will be taken at the investigational site under the supervision of the investigator and/or an authorised and trained designee. Therefore, actual dosing is expected to precisely follow the assigned dose. Dosing will be recorded in the eCRF.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Tumour assessment

Tumour response will be evaluated according to RECIST version 1.1 [R09-0262]. **As of Global Amendment 5, imaging-related endpoints will no longer be assessed by central independent review.**

Patient management-related decisions (continuation on the trial for an individual patient) will be based on investigator assessment (in addition to safety).

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Tumour assessments performed prior to the informed consent as part of routine clinical practice will be accepted if they meet the requirements of the clinical trial protocol and are performed within the screening visit window.

Baseline imaging should include imaging of all known or suspected sites of disease using an appropriate method (e.g. CT scan, MRI, ultrasound), as well as brain scan at screening. The investigator (or designee) will record the target and non-target lesions in the eCRF. Lesions in previously irradiated areas may not be considered measurable at baseline unless the lesions occurred or progressed after irradiation. The same method of assessment and the same imaging technique must be used at each subsequent timepoint to characterise each reported lesion throughout treatment and during follow-up. Photo documentation of superficial lesions should be provided.

In patients who only have 1 target lesion, and where a fresh biopsy of this lesion is required during the screening period, the baseline imaging must be performed before the biopsy or at least 2 weeks after the biopsy.

all imaging-related primary and secondary endpoints will also be assessed by central independent review according to RECIST version 1.1. Instructions for obtaining images and the shipment / transfer of image data will be provided in the imaging manual in the ISF.

Tumour assessments will be performed at the timepoints indicated in the Flowchart. The imaging schedule will be independent of treatment cycles and will be conducted until confirmation of objective disease progression by investigator assessment. The tumour assessment schedule should not change for any reason, including interruption / delay of treatment. Additional unscheduled tumour assessments may be performed at the investigator's discretion. If the patient stops trial medication for a reason other than disease progression, tumour assessment according to RECIST version 1.1 will continue until disease progression by investigator assessment (or until death, lost to follow-up, or end of the trial).

Clinical imaging data acquired in this trial might also be analysed further using exploratory, quantitative approaches. If such exploratory analyses are conducted, then the exploratory analyses may be performed in collaboration with an independent third party nominated by the sponsor.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A physical examination will be performed at the timepoints specified in the Flowchart. It includes as a minimum general appearance, a clinical tumour assessment, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Measurement of height (in cm), body weight (in kg) and the evaluation of the ECOG performance status will be performed at the timepoints specified in the Flowchart.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs (body temperature, systolic and diastolic blood pressure, and pulse rate) will be recorded at the time points specified in the Flowchart, prior to blood sampling and trial drug

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administration. Vital signs measurement will be performed after 2 minutes of supine rest. If the patient cannot rest in a supine position, a rest in a sitting position is acceptable.

5.2.3 Safety laboratory parameters

Safety laboratory parameters will be analysed at a local laboratory at the time points specified in the Flowchart. Safety laboratory examinations will include tests as listed in Table 2. Patients do not have to be fasted for the blood sampling for safety laboratory tests.

Table 2 Safety laboratory tests

Category	Parameters
Haematology	Haemoglobin, red blood cell count, haematocrit, mean corpuscular volume, white blood cell count, and differential blood count (preferably expressed in absolute values), and platelets.
Biochemistry	Glucose, sodium, potassium, chloride, calcium, phosphate, total protein, albumin, uric acid and creatinine kinase (CK; if CK is elevated, then patient should be further evaluated according to local standard of care). If symptoms of pancreatitis are observed, amylase and lipase should be tested at the discretion of the investigator. C-reactive protein (CRP) level should be measured. **Liver function** Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, lactate dehydrogenase, bilirubin (direct and indirect bilirubin in case of elevated total bilirubin values) **Renal function** Blood urea or blood urea nitrogen, and creatinine. Note: Creatinine must be assessed using methods with calibration traceable to IDMS. To assess eligibility during screening, estimated Glomerular Filtration Rate (eGFR) will be calculated (using Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation [Caucasian and Black: R12-1392, Japanese: R22-1536, Other races: R22-1535]). Alternatively, creatinine clearance may be measured using a 24-hour urine collection test.
Coagulation	Activated partial thromboplastin time (aPTT) and prothrombin time (PT) (expressed either in seconds or as percentage) or International Normalised Ratio (INR)
Urinalysis	pH, glucose, erythrocytes, leukocytes, protein, and nitrite analysed by dipstick (semi-quantitative measurements)
Pregnancy	Beta human chorionic gonadotropin (β-HCG) pregnancy test in serum performed for women of childbearing potential at Screening Urine or serum test performed within 72 h prior to start of trial treatment, prior to treatment on Day 1 of every cycle from Cycle 2 Day 1 onwards, at EOT, and then monthly until 6 months after the last dose of treatment.

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Additional parameters may be measured if they are part of the standard panel of the institution laboratory. The investigator should complete additional evaluations of laboratory tests as clinically indicated. Any clinically relevant abnormal finding from these investigations will be reported as an Adverse Event.

In case the criteria for possible potential severe DILI are fulfilled, several additional tests will be performed (please see Section 5.2.6.1 and the "DILI Checklist" provided in the ISF). The total amount of blood taken from the patient will be increased due to this additional sampling.

5.2.4 Electrocardiogram

A 12-lead resting ECG will be performed at the timepoints indicated in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

To minimise interference with the ECG recording, the patient should rest for at least 10 minutes before starting ECG recordings and PK samples should be taken after performing the ECG.

5.2.5 Other safety parameters

Not applicable for this trial.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this clinical trial protocol.

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an AE or SAE (see Section 5.2.6.1.2):

- Worsening of the underlying disease if certain conditions are met; refer to Section 5.2.6.2.4.

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- Worsening of pre-existing conditions other than the underlying disease.
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.

The latest list of “Always Serious AEs” can be found in the EDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Every occurrence of cancer of new histology must be classified as a serious event regardless of the time since the discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections “AE Collection” and “AE reporting to sponsor and timelines”.

5.2.6.1.4 Adverse events of special interest

The term ‘adverse events of special interest’ (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor’s

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Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

In this trial, hepatic injury, specified haematological AEs, and specified gastrointestinal AEs are considered as AESIs. Details are provided below:

Hepatic injury

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

For patients with normal ALT and AST levels at baseline:

- An elevation of AST and / or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT and / or AST elevations ≥10-fold ULN.

For patients with abnormal aminotransaminase levels between >1 and <3-fold ULN at baseline:

- An elevation of AST and / or ALT ≥3-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN (if bilirubin is normal at baseline) or ≥2-fold the baseline value (if bilirubin is elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other

  or

- Aminotransferase elevations (ALT and / or AST ≥5-fold the baseline value).

For patients with abnormal aminotransaminase levels between ≥3-fold ULN and <5-fold ULN at baseline:

- An elevation of AST and / or ALT ≥2-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN (if bilirubin is normal at baseline) or ≥2-fold the baseline value (if bilirubin is elevated at baseline); measured in the same blood sample or in samples drawn within 30 days of each other

  or

- Aminotransferase elevations (ALT and / or AST ≥3-fold the baseline value).

These laboratory findings constitute a hepatic injury alert and the patients showing these laboratory abnormalities need to be followed up according to the “DILI checklist” provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

For further details on potential severe DILI reporting, see Figure 3.

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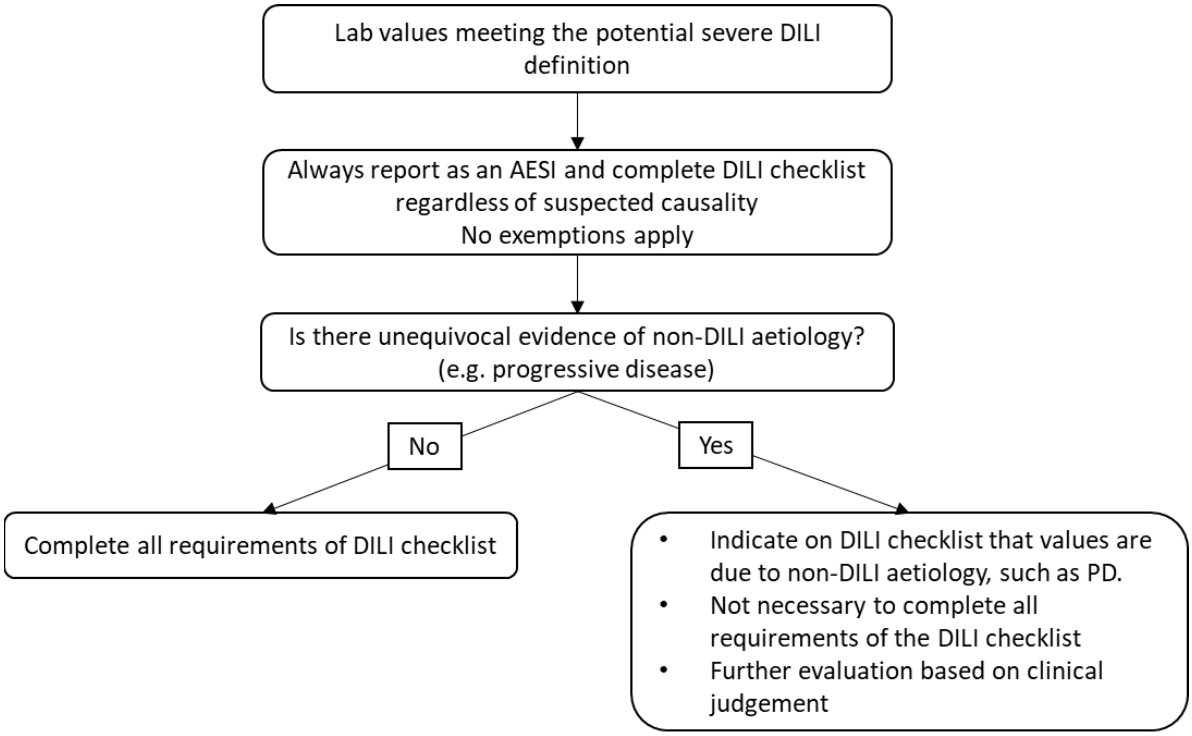


Figure 3 Potential severe DILI reporting

Haematological AEs

- Thrombocytopenia of CTCAE Grade 3 associated with bleeding
- Thrombocytopenia of CTCAE Grade 4
- Neutropenia of CTCAE Grade 3 with documented infection
- Neutropenia of CTCAE Grade 4 lasting >7 days
- Febrile neutropenia CTCAE Grade ≥3
- Thrombocytopenia or anemia requiring transfusion per local or international guidelines

Gastrointestinal AEs

- Nausea of CTCAE Grade ≥3
- Vomiting of CTCAE Grade ≥3
- Diarrhoea/colitis of CTCAE Grade ≥3

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

If the CTCAE grade of an AE increases, a new separate AE should be recorded in the eCRF.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of

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reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the trial drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

Per default, SAEs / AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the BI paper SAE form should be used, please see Section 5.2.6.2.2. The following must be collected and documented:

- From signing the informed consent onwards until the safety follow-up visit (end of REP): all AEs (non-serious and serious) and all AESIs. **If a patient receives brigimadlin in another clinical trial, safety follow-up in this trial will end, and safety follow-up will continue uninterrupted in the new trial.**

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- After the safety follow-up visit (end of REP) while the patient is still followed up for progressive disease: cancers of new histology, all trial drug related SAEs and all trial drug related AESIs.
- After the safety follow-up visit (end of REP) and confirmed progressive disease: the investigator does not need to actively monitor the patient for new AEs but should report any occurrence of cancer of new histology and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

The rules for Adverse Event Reporting exemptions still apply, please see Section 5.2.6.2.4.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages to the sponsor's unique entry point within 24 hours of becoming aware of the event, the country-specific process will be described in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could in addition inform the sponsor upfront via telephone.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

Should the EDC system not be available for more than 24 hours, reporting must occur via the BI paper SAE forms.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial-specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Clinical Studies is to be completed. However, an SAE and / or AESI associated with the pregnancy must be reported as described in Section 5.2.6.2.2.

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5.2.6.2.4 Exemptions to AE / SAE reporting

The occurrence of disease progression is recorded as part of the assessment of trial endpoints for the analysis of efficacy. The following rules will be followed for reporting disease progression and associated signs and symptoms for the analysis of safety:

- Non-serious, asymptomatic disease progression which is unrelated to trial medication is exempted from AE reporting. In this case, disease progression will only be recorded on the response assessment page of the eCRF.
- In other cases of disease progression, the signs and symptoms (and not the term 'disease progression' itself) will be reported on the AE eCRF and reported via the SAE form if applicable.
- If signs and symptoms are attributable to a diagnosis (other than 'disease progression'), reporting the diagnostic term is preferable e.g. pulmonary embolism rather than dyspnoea, intestinal obstruction rather than abdominal pain.
- Lab values meeting the potential severe DILI definition in Section 5.2.6.1.4 must always be reported as AESI, even if the most likely cause is disease progression. No exemption to AE reporting applies.

Exempted events are reviewed at appropriate intervals by the sponsor and the DMC.

Protocol specified exempted events should be collected on the appropriate eCRF page only.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

As of Global Amendment 5, sampling and analyses for pharmacokinetics of brigimadlin will be discontinued; this section is no longer applicable.

5.3.1 Assessment of pharmacokinetics

Pharmacokinetics of brigimadlin will be determined after a single dose administration in Cycle 1. If data allow, PK parameters of brigimadlin after single administration will be evaluated as described in Section 7.2.5 using non-compartmental analysis methods according to BI internal guidelines. If deemed necessary and feasible, further PK parameters may be calculated.

PK assessment will be done to characterise the PK in the target population.

Sparse samples will be collected for determination of brigimadlin concentrations and may be additionally analysed using population pharmacokinetic approaches. For this purpose, data may also be combined with data from other trials. Pharmacometric modelling activities will be planned and documented separately according to internal and external guidelines and SOPs.

Plasma samples may be used for the measurement of unbound drug concentrations. For this purpose, pooled plasma samples may be used. Results may be included in a separate report.

For planned individual plasma concentration sampling times, refer to Appendix 10.2. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of pharmacokinetic parameters.

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5.3.2 Methods of sample collection

Blood samples for analysis of brigimadlin concentrations will be taken as indicated in the Flowchart and Appendix 10.2. Details about sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage and shipment will be provided in the Laboratory Manual. Correct, complete, and legible documentation of drug administrations and blood sampling times, as well as adequate handling and identification of PK samples are mandatory to obtain data of adequate quality for the PK analysis.

After analysis of PK plasma samples, samples may be used for further methodological investigations (e.g., for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

Further details of sample requirements, collection, processing, handling, and shipment are provided in the Laboratory Manual.

5.3.3 Analytical determinations

Brigimadlin will be quantified using a validated liquid chromatography mass spectrometry (LC/MS) assay. All details of the analytical method will be available prior to the start of sample analysis. The analyses will be performed at Boehringer Ingelheim and/or a CRO with given authorization by BI.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

As for pharmacokinetic analysis, pharmacokinetic and pharmacodynamic data may be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOPs.

5.4 ASSESSMENT OF BIOMARKER(S)

As of Global Amendment 5, analyses of exploratory biomarkers will be discontinued; this section is no longer applicable.

This section refers to exploratory biomarkers. Planned exploratory analyses of biomarkers during the trial may be reduced or stopped based on new information in the literature or early analyses.

5.4.1 General handling of samples and biomarker results

Detailed instructions for handling, storage, and shipment of the biomarker samples will be provided in the laboratory manual included in the ISF. All required materials and labels will be provided. If local regulations allow it, any excess materials at the central laboratory will be shipped and stored at BI's central laboratory until all required validations have taken place or

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until it is decided that there is no requirement for validation. Samples will be destroyed no later than 5 years after trial completion.

A brief description of the biomarker analyses to be performed is provided below. All tumour and blood samples will be obtained at the time points specified in the Flowchart.

Eligibility for participation in the trial will be assessed using results from local testing (including tests performed at an external laboratory). Test results from a liquid biopsy are not acceptable.

If a patient withdraws consent, all data already collected up to the time of consent withdrawal will still be used, including data collected at the end of treatment and at the end of trial. However, samples collected and not yet analysed will be destroyed. The pharmacogenetic samples will not be stored upon completion of the genotype analysis and will be destroyed before the end of the clinical trial.

5.4.2 Tumour tissue samples

5.4.2.1 Tumour tissue samples at screening and at EOT

Patients with a written pathology report / molecular profiling report indicating MDM2 amplification and TP53 wild-type status are eligible for enrolment into the trial (see Section 3.3.2).

A sample of archival tumour tissue must be provided for every treated patient. Tumour samples should be a formalin-fixed paraffin embedded (FFPE) block or slides. A tumour block is preferred but slides (minimum 15 slides, ideally 25 slides [or equivalent if agreed with the sponsor]) are acceptable. Please refer to the laboratory manual for further details on sample preparation. The sample should be from the most recently collected tissue wherever possible.

Tumour samples will be used for the retrospective testing of MDM2 amplification and TP53 status. They will be used for co-development of a companion diagnostic test. [redacted] If the molecular pathology test for eligibility has been performed by a vendor designated by the sponsor using the same test as the one used for development of the diagnostic test, the submission of a tissue sample may not be required. The detailed conditions for exempting the tissue sample submission are provided in the laboratory manual.

At EOT, patients will be asked to provide an optional fresh tumour sample. Cohort 1-CN is exempted from this optional fresh tumour biopsy. [redacted]

5.4.2.2 Tumour tissue sample processing and storage

Refer to the laboratory manual for additional details regarding the sample collection, processing, handling, and shipment of the tumour samples.

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5.4.3 Circulating tumour DNA

The isolation of DNA from blood originating from the tumour (circulating tumour DNA, or ctDNA) provides a minimally invasive means of monitoring changes in the biology of the tumour resulting from the trial medication. [redacted] Plasma samples will be destroyed no later than 5 years after trial completion.

5.4.4 Circulating biomarkers

The TP53 pathway also controls the expression of short-length RNA species called microRNAs (miRNA) such as (but not limited to) miRNA-145, miRNA-34, or miRNA-192.

[redacted]

5.4.5 Circulating proteins

Circulating proteins such as cytokines, chemokines, and hormones will be measured to determine the potential predictive or pharmacodynamic impact of these biomarkers on the treatment benefit. Cohort 1-CN is exempted from the circulating proteins measurement.

Longitudinal plasma samples will be used to quantitate the circulating markers and correlative studies will be conducted. Patients will be requested to provide samples of blood prior to their first treatment and periodically thereafter during the treatment period (please refer to the Flowchart).

5.4.6 Pharmacogenetics

Pharmacogenetics (PGx) investigates genetic variations in patients to explain and to predict their individual response to drugs. The pharmacogenetic analysis is mandatory but a whole genome sequencing is excluded.

[redacted]

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5.4.7 Pharmacodynamics marker

Samples taken to determine modulation of GDF-15 will be used to describe the PK/PD relationship. Details of time points for sample collection are specified in the Flowchart.

5.4.8 Tumour markers

Samples taken to determine modulation of CA 19-9 and CEA will be used to describe the PK/PD relationship. CA 19-9 and CEA will be tested locally at time points specified in the Flowchart.

5.5 BIOBANKING

Not applicable for this trial.

5.6 OTHER ASSESSMENTS

5.6.1 Demographics and history

Demographic information including gender, year of birth and race/ethnicity (where allowed according to local law) as well as general medical history (including smoking history, for Cohort 3 only) and detailed oncological disease history will be collected. This will include e.g. date of first diagnosis of malignancy, staging and grading information, details of previous treatment for malignancy, and pre-existing tumour molecular marker information (e.g. Next Generation Sequencing data) where possible.

5.6.2 Patient-reported outcomes

As of Global Amendment 5, patient-reported outcome questionnaires will be discontinued; this section is no longer applicable.

Patient-reported outcomes (PRO) will be measured throughout the trial using the below multidimensional questionnaires. Patients will use digital devices to complete the questionnaires. The sponsor and investigators will endeavour to ensure that PRO data is collected from every patient at every timepoint. In the unlikely event that PRO data cannot be collected for an individual patient or timepoint, the sponsor may agree that the PRO data collection is not required.

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- EORTC QLQ C30 is a questionnaire specific for the assessment of Health related QoL in patients with cancer [R07-2064; R99-1213].
- EORTC IL46 (item 168) is a validated single-item question that assesses overall side effect impact.
- The Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are single-item, FDA-recommended anchors to detect meaningful change [R21-2016].
- Cohorts 1 and 1-CN (biliary tract adenocarcinoma): EORTC QLQ-BIL21 is a questionnaire specific for the assessment of quality of life in patients with cholangiocarcinoma and cancer of the gallbladder.
- Cohort 2 (pancreatic ductal adenocarcinoma): EORTC QLQ-PAN26 is a questionnaire specific for the assessment of quality of life in patients with pancreatic cancer.
- Cohort 3 (lung adenocarcinoma): NSCLC-SAQ is a questionnaire specific for the assessment of quality of life in patients with lung cancer.

The questionnaires will be completed at the time points specified in the Flowchart. To minimize the possibility of bias, on clinic days it is recommended that patients should complete the questionnaires prior to seeing the clinician, prior to clinical assessment, prior to any treatment at the clinic, and before provision of any new information about their disease status. The responses recorded on the questionnaires will not be recorded as adverse events. Adverse events are collected during protocol specified trial visits with the clinician.

The questionnaires generally take about 15 to 30 minutes to complete. Validated translations exist for all questionnaires for all countries participating in the trial, and patients will receive the questionnaires in their native language.

Efforts will be made to ensure questionnaires are available for all patients who wish to participate in the trial. In cases where questionnaires are not available, and depending on the circumstances, the sponsor may agree with the investigator that the patient is not required to complete a single questionnaire or all questionnaires.

EORTC QLQ-C30

The QLQ-C30 comprises 30 questions. The QLQ-C30 incorporates both multi-items scales and single-item measures. These include 1 global health status/QoL scale, 5 functional scales, 3 symptoms scales and 6 single items to assess dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties. Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

PGIS and PGIC

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) are FDA-recommended anchors to detect meaningful change. Both single item PROMs are scored through a Likert response scale: the PGIS is scored on a 4-point Likert scale (1 = none, 4 = severe) while the PGIC is scored on a 5-point Likert scale (1 = much better, 5 = much worse).

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5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used are standard. Safety is assessed based on toxicities graded according to CTCAE version 5.0 [R18-1357]. The CTCAE criteria are commonly used in the assessment of AEs in patients with. RECIST version 1.1 [R09-0262] is used for the evaluation of tumour response. These criteria are well-established and scientifically accepted for evaluating efficacy endpoints.

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6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war), the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

Written informed consent must be obtained before any protocol-specific screening assessments are performed. Informed consent may be signed by the patient prior to the screening visit. Imaging scans performed as part of routine clinical practice and prior to provision of informed consent and within the screening timeframe can be used if they meet the imaging requirements.

Eligible patients will enter the trial and will receive the assigned trial medication until any of the criteria for stopping medication is met (see Section 3.3.4.1).

During the treatment phase, visits should be performed as indicated in the Flowchart. The scheduled time interval for each visit is relative to the initiation of trial medication (CxD1). Following discontinuation of trial medication, an EOT visit must occur as soon as possible (within 7 days after the EOT decision). After the EOT visit, the patient must undergo a follow-up safety evaluation (after the REP). Then the patient will enter the follow-up period until trial completion. Please see the Flowchart for the detailed visit schedule.

Unscheduled visits can be performed as necessary, and assessments will be performed as required at the investigator's discretion. If a patient missed a visit and the patient reports to the investigator between the missed visit and the next scheduled visit, the date of the report and the reason for the delayed visit should be noted in the patient's chart. The next visit, however, should take place at the scheduled time. In the event of any interruption / delay of treatment, the imaging schedule should not be changed.

In COVID-19-related or similar exceptional situations, sites should adhere to the required protocol procedures as close as possible while implementing measures to reduce the risk of transmission of infections; however, where a patient is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor. Patient safety must be ensured when determining if a visit may be remote.

The investigator may organise for routine safety laboratory tests to be performed at a facility which is more convenient for the patient. If this occurs, it is the responsibility of the investigator to ensure compliance with the protocol, GCP, and any local laws and regulations.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

An overview of all assessments to be performed at the respective visit is given in the Flowchart; detailed explanations of procedures or observations are given in Section 5.

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6.2.1 Screening

The screening visit should be performed between 28 days and 1 day prior to first administration of treatment. The screening visit may be performed over multiple days as long as all assessments are within the allowed window.

Before or during the screening visit, prior to any trial procedures, all patients will need to sign the Informed Consent Form (ICF) for trial participation.

Examinations and assessments will be conducted as detailed in the Flowchart. Patients' medical history and demographic information will be collected, and inclusion and exclusion criteria must be assessed (see details below).

A tumour-tissue will be submitted to the central laboratory. This is a mandatory requirement for trial enrolment.

Demographics
During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female to describe the subject's sex at birth)
- For women: of childbearing potential yes / no to characterise the patient population and as a basis for contraception requirements
- Ethnicity and race to sufficiently characterise the patient population, to support possible subgroup analyses, unless not acceptable according to local regulations.

Baseline Conditions
Baseline conditions and concomitant therapies present during screening will be recorded in the eCRF.

Medical History
Medical history for each tumour type will be obtained during screening and documented in the eCRF, this includes:

- Date of first histological diagnosis
- Primary tumour site (including subsite information, e.g., for biliary tract cancer, subsites include intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullar cancer)
- Number and location of metastatic sites at screening (bone, brain, liver, pleural effusion, other)
- Previous anti-cancer treatments including any surgery, radiotherapy, and or systemic therapy, including start and end dates as well as the outcome. If available, the last 2 tumour scans prior to baseline in this trial should be uploaded to the central image repository.
- Tumour response data from previous anti-cancer treatment as available.

Pre-existing tumour molecular marker information (e.g. Next Generation Sequencing data) will be collected where possible.

For Cohorts 1 and 1-CN, history of primary sclerosing cholangitis and liver fluke infection will be collected in the eCRF.

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For Cohort 3 smoking history will be collected.

Baseline imaging
Imaging scans performed as part of routine clinical practice prior to provision of informed consent and within the screening timeframe can be used if they meet the imaging requirements, provided it is clear from source documents that the imaging was not performed for the purpose of the present trial.

6.2.2 Treatment period

Eligible patients will enter the trial and will be administered trial medication in 21-day treatment cycles until criteria for treatment discontinuation are met (see Section 3.3.4). Treatment visits are specified in the Flowchart and must be conducted as scheduled and outlined there.

All procedures will be conducted on Day 1 of the cycle. Selected procedures as well as pharmacokinetics and pharmacodynamics sampling (refer to Appendix 10.2) will also be performed on subsequent days (Days 8 and 15). A treatment delay should not affect the imaging schedule and the PROM schedule – the imaging schedule and the PROM schedule continue, based on the C1D1 date.

6.2.3 Follow-up period and trial completion

6.2.3.1 End-of-Treatment visit (EOT)

All patients must, after permanent discontinuation of trial medication for any reason, perform the EOT visit as soon as possible and within 7 days after EOT decision.

If the decision to permanently discontinue trial medication is taken during a scheduled visit, the EOT visit should be performed instead of the scheduled visit. In the event of early discontinuation for reasons other than confirmed progressive disease, the tumour assessment schedule as outlined in Section 5.1.1 should continue to be followed. If the decision to permanently discontinue is made >35 days after dosing (i.e. following a dose delay) the FU for Safety visit will take place as soon as possible but will be >35 days after last dose. In this situation the EOT visit and the FU for Safety visit may be combined.

After permanent discontinuation of trial medication, further therapy will be decided by the investigator.

6.2.3.2 Safety follow-up visit

After the last administration of trial medication, all patients are required to attend the safety follow-up visit. This visit is conducted as indicated in the Flowchart. The purpose of this visit is primarily to collect all new AEs that occurred after the last administration of trial medication and to follow-up on ongoing adverse events. The safety follow-up visit should occur for all patients, including those patients with confirmed disease progression and / or start of subsequent anti-cancer treatment. For AE reporting after EOT, see Section 5.2.6.2.2.

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6.2.3.3 Follow-up period

As of Global Amendment 5, patients will continue to be followed up for safety as described in Section 5.2 but after treatment discontinuation will no longer be followed up for disease progression and overall survival.

If a patient does not have documented objective disease progression by investigator assessment prior to or at the safety follow-up visit, he / she will continue to have regular follow-up visits (FU-PD) and tumour assessments in accordance with the trial schedule. Assessments will be performed as indicated on the Flowchart. The end of FU-PD will occur at the timepoint of the earliest event of the following:

- Objective disease progression
- Start of further anti-cancer treatment
- Loss to follow-up
- Death
- End of the whole trial as specified in Section 8.6

Follow-up for Progressive Disease (FU-PD), every 6 weeks (until week 48) or 12 weeks (after week 48):

For patients who discontinue for a reason other than confirmed objective disease progression by investigator assessment, follow-up visits continue per the imaging schedule (refer to Section 5.1.1), until confirmed objective disease progression by investigator assessment, lost to follow up, start of subsequent anti-cancer treatment, withdrawal of consent, or completion of the entire trial as specified in Section 8.6.

- For each reportable SAE/AESI, the investigator should provide the information about concomitant medication and the medication administered to treat the AE on the appropriate CRF pages and the SAE form including trade name, indication, and dates of administration.
- Perform tumour imaging and assessment.
- Pregnancy testing as required according to the Flowchart.

During this period, imaging scans will continue to be collected as per the imaging manual and submitted to central imaging laboratory.

Follow-up for survival (FU-OS), every 12 weeks:

After objective disease progression or start of further anti-cancer treatment, the patient will enter the follow-up for survival. No visits will be performed for the purposes of the trial, but data on further anti-cancer treatment and survival will be collected from medical records or via telephone. For WOCBP, pregnancy testing will continue as applicable and according to the Flowchart. Data will be collected every 12 weeks (±7 days) and may also be collected at additional timepoints when a snapshot of data is required (e.g. at the time of analysis). Data collection will continue until death, lost to follow-up, withdrawal of consent, or end of the whole trial (see Section 8.6).

The following information will be collected during the FU-OS period:

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- Date of contact
- Subsequent anti-cancer therapy (if applicable)
- Related SAE / AESI and concomitant medication
- Outcome (date and cause of death, if applicable; for PD, the actual date of PD)

6.2.4 Treatment beyond progression

In case of continued clinical benefit judged by the investigator (e.g., absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumour compression, spinal cord compression] requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment), and based on careful clinical assessment, patients may be allowed to continue brigimadlin beyond disease progression as defined by RECIST version 1.1 criteria. Clinical benefit can include, but will not be restricted to, significant symptom control of originally symptomatic tumours. Patients must provide consent to receive treatment beyond progression and will continue to follow the trial schedule for treatment visits (see Flowchart) including the imaging and clinical tumour evaluations. Central assessment of images will continue. Trial treatment may be continued as long as it is judged beneficial by the investigator.

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The overall trial design is an open-label, single-arm, seamless Phase IIa/IIb trial design to assess brigimadlin monotherapy in multiple cohorts of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type solid tumours.

The primary objectives for the proposed cohorts are to evaluate the efficacy of brigimadlin in patients with the corresponding locally advanced or metastatic, MDM2 amplified, TP53 wild-type tumour types. The primary endpoints are the objective response (OR) based on central independent review.

Cohort 1 (biliary tract adenocarcinoma):

The primary endpoint OR will be assessed at 2 timepoints: (1) at the interim futility analysis when the first 30 treated patients have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier; and (2) at the final primary endpoint analysis when all treated patients (approximately 90 patients) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier. The primary endpoint objective response will be analysed in terms of confirmed ORR (based on central independent review), defined as the proportion of patients with a best overall response of CR or PR.

Cohort 1-CN (biliary tract adenocarcinoma):

The primary endpoint OR will be assessed when all treated patients in this cohort (approximately 25 patients) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier. The primary endpoint objective response will be analysed in terms of confirmed ORR (based on central independent review), defined as the proportion of patients with a best overall response of CR or PR.

Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, and urothelial bladder cancer):

For the primary endpoint OR, the proportion of patients with a best overall response of CR or PR will be analysed when all treated patients (approximately 10 patients for Cohort 2, and approximately 15 patients for Cohorts 3 and 4) have been followed for at least 12 weeks (or 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Hypothesis testing will no longer be conducted as a result of the decision to discontinue development of brigimadlin.

Cohort 1 (biliary tract adenocarcinoma):

In Cohort 1, the trial main objective as described in Section 2.1.1 will be evaluated by 2 statistical objectives described below.

- Statistical objective 1

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The first statistical objective is to show superiority of brigimadlin monotherapy over historical benchmark from current available treatment options using ORR. Given that the treatment options for patients with locally advanced or metastatic biliary tract adenocarcinoma are limited and often consist of several, subsequent chemotherapies that are not suitable for many patients and show minimal efficacy, the ORR of 5% for FOLFOX (a category 2A recommendation by NCCN for 2nd line treatment) is considered as the response rate of the current best treatment option and used as a null hypothesis [R22-0948].

A statistical testing of ORR against the null hypothesis based on the binomial distribution will be conducted and the corresponding p-value will be compared with a significance level of 2.5%.

- Statistical objective 2

The clinical value of brigimadlin monotherapy depends on the degree of improved efficacy over the current treatment options. Therefore, the statistical objective 2 is to show definitive clinically meaningful efficacy of brigimadlin monotherapy using ORR. The observed ORR will be compared with a pre-specified critical value of 23.3% (21/90).

Decision criterion for statistical objective 1

The null and alternative hypothesis for the primary endpoint, objective response, is

H_0: Effect of brigimadlin on the percentage of patients with objective response, ORR ≤5%;

versus the alternative hypothesis

H_A: Effect of brigimadlin on the percentage of patients with objective response, ORR >5%.

Only if the null hypothesis H_0 is rejected at the final primary endpoint analysis, will brigimadlin monotherapy be considered better than the current best treatment option.

Decision criterion for statistical objective 2

Only if observed ORR ≥23.3% at the final primary endpoint analysis, will brigimadlin show definitive clinically meaningful efficacy.

Additionally, for the primary endpoint OR, an interim futility analysis is planned using a non-binding futility boundary of confirmed ORR = 20%. There is no plan to test or claim for superiority at the interim futility analysis. Therefore, no alpha will be spent at the interim futility analysis. Details for the interim analysis are described in Section 7.2.8.

Cohort 1-CN (biliary tract adenocarcinoma):

No hypothesis testing is planned for this cohort.

Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, and urothelial bladder cancer):

No hypothesis testing is planned for these cohorts.

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7.2 PLANNED ANALYSES

7.2.1 General considerations

In this trial, different cohorts will be analysed separately, i.e. Cohort 1, Cohort 1-CN, Cohort 2, Cohort 3, and Cohort 4. Besides these, pooled analyses for data from Cohort 1 and Cohort 1-CN will be conducted for all BTC patients.

In each set of analyses for Cohort 1 only, Cohort 1-CN only, and Cohorts 1 and 1-CN (pooling data from Cohort 1 and Cohort 1-CN), there will be 3 main patient populations for the analyses: the treated set (TS), the efficacy analysis set, and the PK set.

- Treated Set (TS)

  This patient set includes all treated patients who have received at least 1 dose of trial medication. This is the main analysis set for the presentation of safety data for Cohort 1 only, Cohort 1-CN only, and Cohorts 1 and 1-CN (pooling data from Cohort 1 and Cohort 1-CN).

- Efficacy Analysis Set

  This patient set includes all treated patients who have received appropriate prior standard of care therapy and have received at least 1 dose of trial medication. This is the analysis set for the presentation of the primary endpoint of ORR for Cohort 1 only, Cohort 1-CN only, and Cohorts 1 and 1-CN. This is also the main analysis set for the presentation of efficacy data for Cohort 1 only, Cohort 1-CN only, and Cohorts 1 and 1-CN.

- PK set – no longer applicable as of Global Amendment 5

  This patient set includes all patients in the TS who provide at least 1 observation for at least 1 PK endpoint without important protocol deviations relevant to the evaluation of PK.

In each set of analyses for Cohorts 2-4, there will be 2 main patient populations for the analyses: the treated set (TS) and the PK set.

- Treated Set (TS)

  This patient set includes all treated patients who have received at least 1 dose of trial medication. This is the main analysis set for the presentation of safety and efficacy data for Cohorts 2-4.

- PK set – no longer applicable as of Global Amendment 5

  This patient set includes all patients in the TS who provide at least 1 observation for at least 1 PK endpoint without important protocol deviations relevant to the evaluation of PK.

Any other analysis sets will be defined in the TSAP, e.g. for the biomarker assessments.

No per protocol set will be used in the analysis for this trial. However, important protocol deviations will be identified and listed in the Clinical Trial Report (CTR).

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7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial (for all cohorts) are:

- Start of subsequent anti-cancer therapy before progressive disease (PD) based on central independent review
- Start of a restricted medication (see Section 4.2.2.1)
- Lost to follow-up
- Withdrawal of informed consent by patient
- Missed visits, or 2 or more consecutively missed tumour assessments
- Treatment discontinuation
- Death

The strategies for handling intercurrent events in this trial (for all cohorts) are as follows:

Primary strategy for OR analysis

The intercurrent events, start of subsequent anti-cancer therapy, loss to follow-up, withdrawal of informed consent, missed visits, or 2 or more consecutively missed tumour assessments before the event of interest occurs, and death will be handled using the "while on treatment strategy" as defined in ICH E9 (R1).

The intercurrent events, treatment discontinuation and start of restricted medications will be handled using the "treatment policy" approach as defined in ICH E9 (R1).

Table 3 Handling of intercurrent events as per ICH E9 (R1) within the different strategies

Intercurrent event	**Primary strategy**
Start of subsequent anti-cancer therapy before a PFS event by central independent review	While on treatment strategy
Start of a restricted medication	Treatment policy
Lost to follow-up	While on treatment strategy
Withdrawal of informed consent by patient	While on treatment strategy
Missed visits, or 2 or more consecutively missed tumour assessments	While on treatment strategy
Treatment discontinuation	Treatment policy
Death	While on treatment strategy

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Any handling of intercurrent events not listed above will be decided during review and documented in the TSAP.

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7.2.3 Primary objective analyses

The primary endpoint of OR is defined in Section 2.1.2.

Cohort 1 (biliary tract adenocarcinoma):

For Cohort 1, the primary endpoint of the trial is objective response (OR), based on central independent review, and will be analysed in terms of OR rate (ORR).

OR is defined as a best overall response of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1 from the date of treatment start until disease progression, death, last evaluable tumour assessment before start of subsequent anti-cancer therapy, loss to follow-up, or withdrawal of consent, whichever occurs first. Each patient will be assigned as having a best overall response of one of the following RECIST categories: CR, PR, SD (stable disease), PD (progressive disease), or NE (not evaluable).

A best overall response of CR or PR must be confirmed by a subsequent tumour assessment, i.e. a confirmed response requires a repeat observation at least 4 weeks apart.

Unconfirmed PR or CR will be presented as a sub-category of confirmed SD. SD must last for at least 35 days to be presented as SD. SD lasting less than 35 days and followed by PD will be presented as a sub-category of PD. SD lasting less than 35 days and without evaluable response thereafter will be listed as a sub-category of “Other”.

Objective response rate (ORR) gives the percentage of patients with objective response. The final primary endpoint analysis will be performed when all enrolled patients have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier.

For the final primary endpoint analysis, proportions of patients with objective response will be presented along with 95% CIs (exact method).

Prior to the final primary endpoint analysis, one formal interim analysis is planned to be performed when the first 30 enrolled patients have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments), or have discontinued tumour assessment earlier (refer to Section 7.2.8).

Cohort 1-CN (biliary tract adenocarcinoma):

For Cohort 1-CN, the primary endpoint of OR (based on central independent review) will be assessed when all treated patients have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments) or have discontinued treatment earlier. Proportions of patients with objective response will be presented with 95% CIs (exact method).

Cohorts 1 and 1-CN (pooling data from Cohort 1 and Cohort 1-CN):

Based on the pooling data from Cohort 1 and Cohort 1-CN, the primary endpoint of OR (based on central independent review) will be assessed when all treated patients from these cohorts have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments) or have discontinued treatment earlier. Proportions of patients with objective response will be presented with 95% CIs (exact method).

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Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, urothelial bladder cancer):

For Cohorts 2-4, the primary endpoint of OR (based on central independent review) will be assessed when all treated patients have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments) or have discontinued treatment earlier. Proportions of patients with objective response will be presented with 95% CIs (exact method).

7.2.3.1 Sensitivity Analyses

There is no pre-defined sensitivity analysis. Sensitivity analyses will be specified in the TSAP, if applicable.

7.2.3.2 Subgroup Analyses

Cohort 1 (biliary tract adenocarcinoma):

For exploratory purposes, subgroup analyses might be performed by factors that might be relevant to efficacy:

- Age
- Sex
- Race
- Region
- Measurable disease at baseline
- ECOG performance status at baseline

Further subgroup analyses may be defined in the TSAP.

Cohort 1-CN (biliary tract adenocarcinoma):

There is no pre-defined subgroup analysis. Subgroup analyses will be specified in the TSAP, if applicable.

Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, urothelial bladder cancer):

There is no pre-defined subgroup analysis. Subgroup analyses will be specified in the TSAP, if applicable.

7.2.3.3 Supplementary Analyses

In addition to the analysis described in Section 7.2.3, the primary endpoint may be analysed using secondary strategies for the handling of intercurrent events as specified in the TSAP.

Details for the supplementary analyses will be provided in the TSAP.

7.2.4 Secondary objective analyses

Cohort 1 (biliary tract adenocarcinoma):

No key secondary endpoints are defined for Cohort 1. For the secondary endpoints definition please refer to Section 2.1.3.

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The following secondary endpoints will be evaluated at the same time as the final primary endpoint analysis: DOR, PFS, and DC. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohort 1, please refer to Section 8.6.

Duration of objective response

Duration of objective response (DOR) is defined as the time interval from first documented confirmed OR until disease progression or death among patients with confirmed objective response (based on central independent review), whichever occurs first.

For all patients with OR the duration of OR will be calculated as follows:

- Duration of OR [days] = date of outcome – date of first assessment of OR + 1

For patients without disease progression or death:

- Duration of OR (censored) [days] = date of outcome – date of first assessment of OR + 1

The censoring rules for DOR are provided in Section 7.3. Only radiological assessments after the first assessment indicating objective response should be taken into consideration. All data after treatment discontinuation, but prior to any subsequent anti-cancer therapy will be included. Detail about the handling of intercurrent events for DOR will be provided in the TSAP.

Kaplan-Meier methods will be used for the calculation of DOR. Further details will be provided in the TSAP, if needed.

Progression-free survival

For patients with known date of progression based on central independent review or death:

- PFS [days] = earlier date of progression based on central independent review or death – date of first treatment + 1.

For patients who will be censored:

- PFS [days] = date of last imaging assessment without disease progression based on central independent review – date of first treatment + 1.

The censoring rules for PFS are provided in Section 7.3. All data after treatment discontinuation, but prior to any subsequent anti-cancer therapy will be included. Data after subsequent anti-cancer therapy will be censored. Details about the handling of intercurrent events for PFS will be provided in the TSAP.

Kaplan-Meier methods will be used for the calculation of PFS. Further details will be provided in the TSAP, if needed.

Overall survival

For patients with known date of death of any cause:

- OS [days] = date of death - date of first treatment + 1.

For patients who died but with unknown date of death of any cause:

- OS [days] = date of last contact when the patient is known to be alive - date of first treatment + 1.

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For patients who will be censored:

- OS [days] = date of last contact when the patient is known to be alive - date of first treatment + 1.

The censoring rules for OS are provided in Section 7.3. All data will be included. Details about the handling of intercurrent events for OS will be provided in the TSAP.

Kaplan-Meier methods will be used for the calculation of OS. Further details will be provided in the TSAP, if needed.

Disease control

Disease control is defined as a best overall response of CR, PR, or SD lasting at least 42 days according to RECIST version 1.1 (based on central independent review). Handling of intercurrent events for DC is the same as for OR.

Proportions of patients with disease control will be presented along with 95% CIs. Further details will be provided in the TSAP, if needed.

Patient-reported outcomes

The EORTC QLQ-C30 questionnaire will be used to collect data on the patient's physical functioning, fatigue, and role functioning status. The EORTC QLQ-BIL21 questionnaire will be used to collect data on the patient's tiredness status. All data after treatment discontinuation, but prior to any subsequent anti-cancer therapy will be included. Details about the handling of intercurrent events for PROs will be provided in the TSAP.

Descriptive statistics (e.g. means and medians) will be used to summarize the individual items and sub-scale scores (i.e. EORTC QLQ-C30 and EORTC QLQ-BIL21) at each scheduled assessment time point. Additionally, the change from baseline in the domain scores at each scheduled assessment time point will be summarised. Further details will be provided in the TSAP, if needed.

Cohort 1-CN (biliary tract adenocarcinoma):

No key secondary endpoints are defined for Cohort 1-CN. For the secondary endpoints definition please refer to Section 2.1.3.

The following secondary endpoints will be evaluated at the same time as the primary endpoint analysis: DOR, PFS, and DC. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohort 1-CN, please refer to Section 8.6.

DOR, PFS, OS, and DC in Cohort 1-CN will be analysed using the same statistical methods as for the corresponding endpoints in Cohort 1.

Cohorts 1 and 1-CN (pooling data from Cohort 1 and Cohort 1-CN):

The following secondary endpoints will be evaluated at the same time as the primary endpoint analysis: DOR, PFS, and DC. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohort 1 or Cohort 1-CN, which comes later.

DOR, PFS, OS, and DC in Cohorts 1 and 1-CN (including additionally pooling data from Cohort 1 and Cohort 1-CN) will be analysed using the same statistical methods as for the corresponding endpoints in Cohort 1.

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Cohorts 2-4 (pancreatic ductal adenocarcinoma, lung adenocarcinoma, urothelial bladder cancer):

No key secondary endpoints are defined for Cohorts 2-4. For the secondary endpoints definition please refer to Section 2.1.3.

The following secondary endpoints will be evaluated at the same time as the final primary endpoint analysis: DOR, PFS, and DC. The secondary endpoint OS will be evaluated at the final analysis at the end of the trial for Cohorts 2-4, please refer to Section 8.6

DOR, PFS, OS, and DC in Cohorts 2-4 will be analysed using the same statistical methods as for the corresponding endpoints in Cohort 1.

7.2.5 Further objective analyses

Further endpoints are defined in Section 2.2.2.

OR based on investigator assessment will be summarised descriptively.

PFS, DOR, and DC based on investigator assessment will be analysed using the same statistical methods as for the corresponding endpoints based on central independent review.

Time to treatment failure

Time to treatment failure (TTF) is defined as the time interval from first treatment administration until the earliest of treatment discontinuation for any reason, including but not limited to disease progression, treatment toxicity, and death.

For patients who discontinue trial medication:

- Time to treatment failure [days] = Date of treatment discontinuation – date of first treatment administration + 1

For patients who did not discontinue trial medication:

- Time to treatment failure (censored) [days] = Date of last drug intake – date of first treatment administration + 1

Biomarker

[redacted]

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.2.2 will be calculated for brigimadlin according to the relevant BI internal procedures.

All patients in the treated set who received at least 1 dose of brigimadlin and provided at least 1 valid plasma concentration value will be included in the pharmacokinetic analysis. Patients who are considered as not evaluable will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations or pharmacokinetic parameters.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the

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pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (i.e. to the same number of decimal places provided in the bioanalytical report).

The following descriptive statistics will be calculated for plasma concentrations: number (N), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. For PK parameters, the tenth percentile (P10), Q1, Q3, and ninetieth percentile (P90) will also be calculated. The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. Thereafter, the individual values, as well as the descriptive statistics, will be reported with 3 significant digits in the CTR.

Patient-reported outcomes

Individual item and sub-scale scores of the EORTC QLQ-C30, EORTC IL46 (item 168), PGIS, PGIC, EORTC QLQ-BIL21 (for Cohorts 1 and 1-CN only), EORTC QLQ-PAN26 (for Cohort 2 only), and NSCLC-SAQ (for Cohort 3 only) questionnaires will be analysed as further endpoints. Details will be provided in the TSAP.

Further details about further objective analyses will be provided in the TSAP.

For handling of missing data, please refer to Section 7.3.

Analyses will be carried out using Phoenix® WinNonlin® 6.3 (or later) and/or SAS® software version 9.4 (or later).

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 30 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation. For more details about the REP, please refer to Section 1.2.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current MedDRA version at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Distribution parameters as well as frequency and percentage of patients with abnormal values or clinically relevant abnormal values will be displayed descriptively.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the trial and at the end-of-trial evaluation will be assessed regarding possible changes compared to findings before start of treatment.

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7.2.7 Other Analyses

To allow for population PK modelling (Section 5.3.1) and exposure-response analysis (Section 5.3.4) ("Fast-track"), dedicated database snapshots may be generated prior to database lock (DBL). This process will be defined in a 'fast-track analysis logistics plan'.

Exploratory analyses of the association between analysed biomarkers and clinical endpoints will be performed. Details will be provided in the TSAP.

7.2.8 Interim Analyses

Interim futility analysis

While recruitment of patients will continue, an interim futility analysis of the primary endpoint OR is planned to be performed for Cohort 1 when the first 30 treated patients have been followed for at least 12 weeks (or have 2 post-baseline tumour assessments) or have discontinued tumour assessment earlier. If Cohort 1 passes the non-binding futility boundary of ORR = 20% for OR (based on central independent review), then Cohort 1 will continue to full enrolment.



DMC analyses

During this open-label trial, an independent DMC will review interim efficacy and safety analyses prepared by the sponsor, at the interim futility analysis and as needed during the conduct of the trial. For more details about the DMC, please see Section 8.7.

A minimum number of sponsor internal team members will review aggregated data before the end of the trial as defined in Section 8.6.

7.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed. Every effort will be made to obtain the date of progression for patients known to have progressed, the date of death for patients known to have died, and complete information on all AEs. For partial or missing AE onset and/or end dates, BI internal rules will be applied for imputation. Patients with unknown vital status, missing tumour imaging data will be censored for time to event analyses as detailed below.

Table 4 describes how patients will be classified for the analysis of PFS. Sensitivity analyses will examine the effect of using alternative rules.

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Table 4 Derivation rules for progression-free survival

Situation	Outcome	Date of outcome
No baseline radiological assessment		
Death on or before the 2nd planned radiological assessment	Event	Date of death
Alive or death after 2nd radiological assessment	Censored	Date of first treatment
Without post-baseline radiological assessments		
Vital status is unknown or known to be alive	Censored	Date of first treatment
Death prior or on the 2nd planned radiological assessment	Event	Date of death
Death beyond the 2nd planned radiological assessment	Censored	Date of first treatment
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed, no more than 1 consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, 2 or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, 0 or 1 missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but 2 or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessment
Death but no progression, 0 or 1 missed radiological assessment prior to death	Event	Date of death
Death without progression, but 2 or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to death	Censored	Date of first treatment

For endpoints related to OR and DC, the rules defined above, where applicable, will be followed.

Table 5 describes how patients will be classified for the analysis of overall survival. Patients will be censored at the date of last contact if the investigator is no longer able to contact a patient or caregiver, and vital status cannot be determined otherwise, provided that no other information indicates that the patient was near death at that point.

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Table 5 Derivation rules for overall survival

Situation at time of analysis	Outcome	Date of outcome
Death and the date of death is known	Event	Date of death
Death and date of death is unknown	Event	Date of last contact when the patient is known to be alive + 1 day
Alive	Censored	Date of last contact when the patient is known to be alive
Unknown	Censored	Date of last contact when the patient is known to be alive

Table 6 describes how patients will be classified for the analysis of DOR.

Table 6 Derivation rules for duration of objective response

Situation	Outcome	Date of outcome
No other anti-cancer therapy		
Alive and not progressed, no more than 1 consecutively missed radiological assessments	Censored	Date of last radiological assessment
Alive and not progressed, 2 or more consecutively missed radiological assessments	Censored	Date of last radiological assessment prior to missed radiological assessments
Progressed, 0 or 1 missed radiological assessment prior to progression	Event	Date of radiological assessment of progression
Progressed, but 2 or more consecutively missed radiological assessments prior to progression	Censored	Date of last radiological assessment prior to missed assessments
Death but no progression, 0 or 1 missed radiological assessment prior to death	Event	Date of death
Death without progression, but 2 or more consecutively missed radiological assessments prior to death	Censored	Date of last radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death, no more than 1 consecutively missed radiological assessments prior to start of subsequent anti-cancer therapy	Censored	Date of last radiological assessment before initiation of subsequent anti-cancer therapy

Plasma concentration - time profiles

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not to the lag phase) will be ignored and not replaced by zero at any time point (including the lag phase).

Pharmacokinetic parameters

In the non-compartmental analysis, concentration data identified with NOS, NOR, and NOA will not be considered. BLQ values in the lag phase will be set to zero. The lag phase is

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defined as the period between time zero and the first time point with a concentration above the quantification limit. All other BLQ values of the profile will be ignored. Every effort will be made to include all concentration data in an analysis. If not possible, a case-to-case decision is required whether the value should be excluded from the analysis.

If a concentration value is excluded from calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the tables in Section 15 of the CTR associated with an appropriate flag.

If the actual sampling time is not recorded or is missing for a certain time point, the planned time will generally be used for this time point instead.

7.4 RANDOMISATION

Not applicable as this is an open-label, single-arm trial.

7.5 DETERMINATION OF SAMPLE SIZE

In November 2024, Boehringer Ingelheim decided to discontinue future development of brigimadlin. Recruitment in 1403-0011 and further expansion of the study, including Cohort-1-CN has been discontinued as of 26 Nov 2024.

Cohort 1 (biliary tract adenocarcinoma):

The overall sample size is approximately 90 patients. An interim futility analysis will occur when the first 30 patients enrolled will become evaluable for ORR (e.g. have been followed until at least the Week 12 tumour assessment or have discontinued treatment earlier due to any reason other than disease progression). Enrolment will continue while waiting for objective response to become evaluable for the first 30 patients. If the futility boundary (observed ORR = 20%) is passed, the trial will continue to full enrolment (i.e. 90 patients).-

Table 7 shows the probability of passing the futility boundary in the interim analysis after the first 30 patients and the probability of passing the pre-specified critical value of statistical objective 2 at the final primary endpoint analysis for different underlying (true) ORR values. This table indicates that with the first 30 patients and the additional 60 patients, the 1-sided error of falsely observing an ORR passing the critical value of 23.3% (statistical objective 2) will be controlled under 0.1% if the true underlying ORR is 5%. Even under the scenario where the true underlying ORR is 15%, the probability of observing an ORR ≥23.3% will be less than 2%. On the other side, the probability of observing an ORR ≥23.3% will be more than 88% under the positive scenarios assuming ORR ≥30%. Overall, 90 patients are considered sufficient for Cohort 1.

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Table 7 Probability of a go decision at the interim futility analysis and success at the final primary endpoint analysis under different scenarios

	Brigimadlin True ORR [%]	**Interim criterion: Observed ORR ≥20% (6/30) Interim Go [%]**	**Final criterion: Observed ORR ≥23.3% (21/90) Final success [%] ***
Scenario 1	5	0.3	<0.1
Scenario 2	10	7.3	<0.1
Scenario 3	15	28.9	2.0
Scenario 4	20	57.2	21.3
Scenario 5	25	79.7	60.9
Scenario 6	30	92.3	88.2
Scenario 7	35	97.7	97.3

* Unconditional power taking futility analysis into consideration.

Cohort 1-CN (biliary tract adenocarcinoma):

Cohort 1-CN will include approximately 25 patients. With this sample size, if the true response rate is 30%, it can show 97.1% probability of consistency with the overall 115 BTC patients in Cohorts 1 and 1-CN (90 patients in Cohort 1 + 25 patients in Cohort 1-CN) by Pharmaceuticals and Medical Devices Agency (PMDA) method 2 (each region showing a similar tendency). Sample size may be re-calculated depending on number of patients with unconfirmed MDM2 amplification.

Cohort 2 (pancreatic ductal adenocarcinoma):

The exploratory Phase IIa part will include approximately 10 patients with locally advanced or metastatic pancreatic ductal adenocarcinoma as a futility analysis. With this sample size, the probability of observing 2 or more responders is no more than 8.6% if the true response rate is 5%.

Cohort 3 (lung adenocarcinoma):

The exploratory Phase IIa part will include approximately 15 patients with advanced/metastatic lung adenocarcinoma as a futility analysis. With this sample size, the probability of observing 5 or more responders is no more than 3.6% if the true response rate is 13%.

Cohort 4 (urothelial bladder cancer):

The exploratory Phase IIa part will include approximately 15 patients with urothelial bladder cancer after first-line progression as a futility analysis. With this sample size, the probability of observing 6 or more responders is no more than 3.9% if the true response rate is 18%.

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8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), EU Regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the CTR. In exceptional cases, data may be published before the CTR, if this is discussed and agreed to by the investigators and the sponsor.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient’s own free will with the informed consent form after confirming that the patient understands the contents. The investigator or his delegate must sign (or place a seal on) and date the informed consent form.

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If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

eCRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the Sponsor or Sponsor appointed CRO (e.g. for tumour related assessments), the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security

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number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication

Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)

Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

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8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site during the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Not applicable for this trial.

8.6 TRIAL MILESTONES

The start of the trial is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The end of the trial for Cohort 1 is defined as the timepoint when all patients treated in Cohort 1 have ended treatment, have completed (or failed to attend) the FU for safety visit, and have been followed up for at least 6 months on survival status or have died before.

The end of the trial for Cohort 1-CN is defined as the timepoint when all patients treated in Cohort 1-CN have ended treatment, have completed (or failed to attend) the FU for safety visit, and have been followed up for at least 6 months on survival status or have died before.

The end of the trial for Cohorts 2-4 is defined as the timepoint when all patients treated in Cohorts 2-4 have ended treatment, have completed (or failed to attend) the FU for safety visit, and have been followed up for at least 6 months on survival status or have died before.

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The "Last Patient Last Treatment" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within 1 year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI). In EU/EEA countries, the trial is sponsored by Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A steering committee (SC) will act as an advisory body and oversees the execution and the dissemination of the trial. It will consist of independent experts, sponsor representatives from different disciplines, and investigator representatives. The composition of the SC will be documented in the Trial Master File (TMF). The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor and will also be summarised in an SC charter.

An independent Data Monitoring Committee (DMC) will be established. Members of the DMC are independent of BI; they are physicians with relevant expertise. The DMC will review the interim efficacy and safety analyses. Details will be provided in a DMC charter. The DMC may initiate a consultation with appropriate experts if additional expertise is needed regarding the evaluation of any safety signals.

Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs) / Health Authorities (HAs), IRBs / ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

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The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader responsible for coordinating all required activities:

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operative Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, a central images service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

The central imaging vendor will conduct independent assessments on a regular basis to support the interim and primary analysis of efficacy endpoints based on RECIST. The imaging vendor’s roles and responsibilities will be described in an imaging charter.

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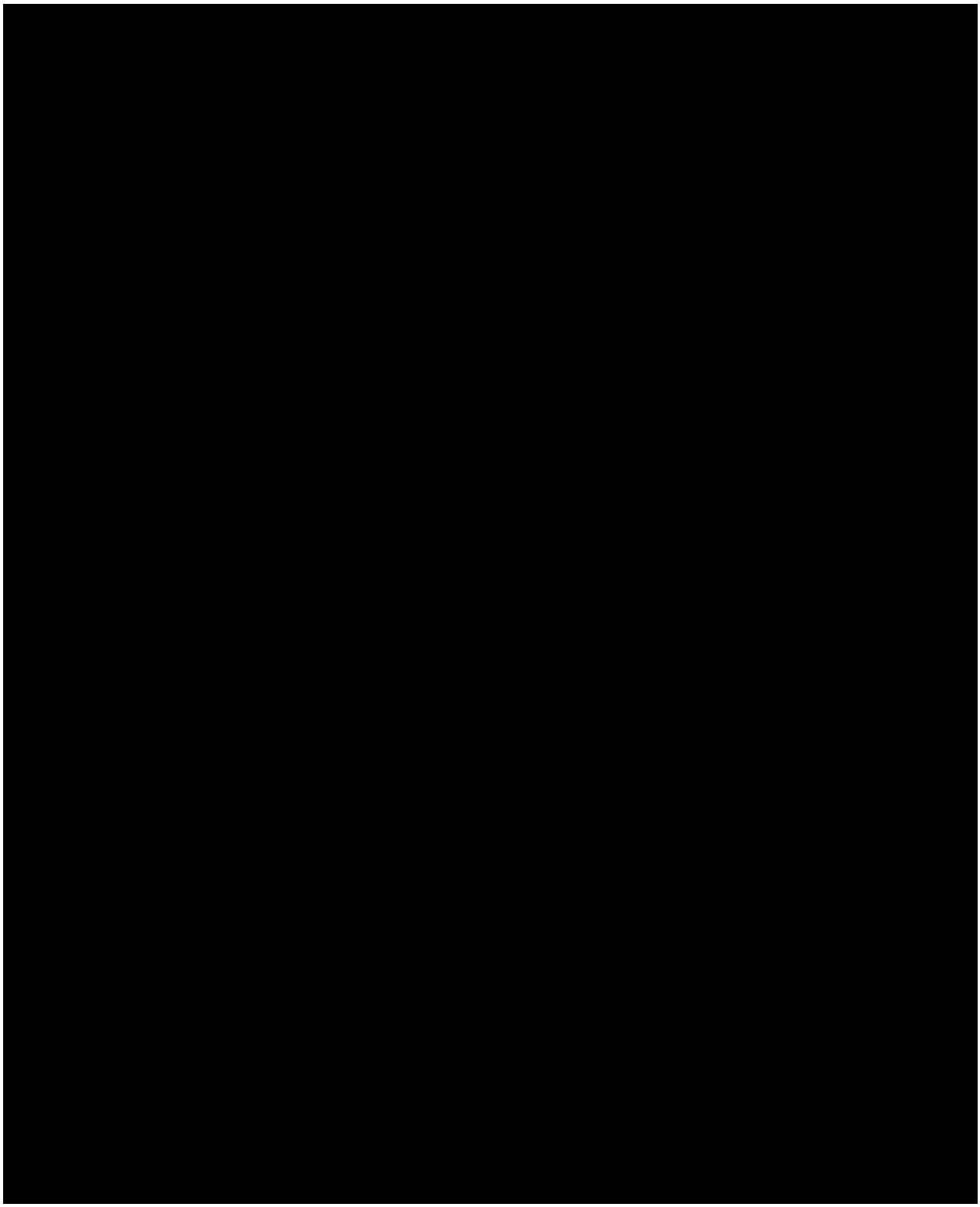
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10. APPENDICES

10.1 RESTRICTED CONCOMITANT MEDICATIONS



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10.2 DETAILED TIME SCHEDULE FOR BLOOD SAMPLING AND ECG ASSESSMENTS – NO LONGER APPLICABLE AS OF GLOBAL AMENDMENT 5

Table 9 Time schedule for blood sampling (brigimadlin PK, GDF-15) and ECG assessments

Cycle	Day	Time Point [hh:min]	CRF Time / PTM	Event	Single 12-lead ECG (prior to PK sampling)	Brigimadlin PK	GDF-15
1	1	Just before drug administration	-0:05	Blood sampling	X	X	X
		Start of brigimadlin intake	0:00	Drug administration			
		1:00	1:00	Blood sampling		X	
		2:00	2:00	Blood sampling		X	
		3:00	3:00	Blood sampling		X	
		4:00	4:00	Blood sampling	X	X	
		6:00	6:00	Blood sampling		X	
		8:00	8:00	Blood sampling		X	X
	8 (±1)	168:00	168:00	Blood sampling		X	X
	15 (±1)	336:00	336:00	Blood sampling		X	X
2	1 (±3)	Just before drug administration	-0:05	Blood sampling		X	X
		Start of brigimadlin intake	0:00	Drug administration			
		4:00	4:00	Blood sampling	X	X	
	8 (±1)	168:00	168:00	Blood sampling		X	X
3 and 4	1 (±3)	Just before drug administration	-0:05	Blood sampling		X	X
		Start of brigimadlin intake	0:00	Drug administration			
		4:00	4:00	Blood sampling	X	X	
≥5 [a]	1 (±3)	Just before drug administration	-0:05	Blood sampling		X	X
		Start of brigimadlin intake	0:00	Drug administration			
		4:00	4:00	Blood sampling	X	X	
EOT				Blood sampling	X		X
FU for safety				Blood sampling	X		

[a] Cycle 5, Cycle 8, Cycle 11, and every 6th cycle thereafter.
General notes:
The following time windows are allowed for brigimadlin PK / GDF-15 biomarker sampling at Cycle 1:
Pre-dose (PTM -0:05): within 1 hour before next drug administration.
1-6 h: within ±10 min of designated time.

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8 h: within ±30 min of designated time
168 h and 336 h: ±24 hours
The following time windows are allowed for brigimadlin PK / GDF-15 biomarker sampling at Cycle 2 and beyond:
Pre-dose (PTM -0:05): within 1 hour before next drug administration.
4 h: within ±10 min of designated time.
168 h ±24 hours
Time windows are specified for procedural reasons; deviations do not automatically lead to exclusion of samples from data evaluation.

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 Oct 2022
EudraCT number **EU number**		2022-001500-18
BI Trial number		1403-0011
BI Investigational Medicinal Product(s)		BI 907828
Title of protocol		Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of BI 907828 for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Synopsis (main inclusion and exclusion criteria), flowchart, sections 3.3.2, 5.4.2.1, and 6.2.1.
Description of change		The requirement of submitting "archival tumour tissue or a fresh biopsy" was updated to submit "archival tumour tissue". In section 5.4.2.1., a statement was added that the sample should be from the most recently collected tumour tissue.
Rationale for change		The previous description might mislead readers to think that the sponsor is proactively collecting fresh biopsy. The investigators may decide, based on the balance between potential benefit and risk for patients, to take a biopsy. However, this is not part of this protocol.
Section to be changed		Flowchart and section 6.2.3.3
Description of change		The time point of follow-up for PD was updated from every 6 weeks to every 6 weeks (until week 48) or 12 weeks (after week 48) weeks.
Rationale for change		Clarification
Section to be changed		Flowchart
Description of change		"(C1)" was added to the whole blood sample for pharmacogenetics at cycle 1 and 2 day 1 column.
Rationale for change		Clarification
Section to be changed		Flowchart

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Description of change		Footnote 19 was added: ECG, blood sampling for PK, and blood sampling for GDF-15 are performed in cycle 5, cycle 8, cycle 11 and every 6th cycle thereafter.
Rationale for change		Clarification
Section to be changed		Section 1.4.2
Description of change		Number of patients treated with BI 907828 so far was updated from 100 to 160.
Rationale for change		Update with latest information.
Section to be changed		Section 1.4.3.1
Description of change		To date, there are no interactions expected between active COVID-19 vaccinations or therapeutics and the use of BI 907828 monotherapy. Patients treated with BI 907828 should be carefully monitored for myelosuppressive side effects induced by the investigational compound before SARS-CoV-2 (severe acute respiratory syndrome-corona virus-2) active vaccination is started as guided in local EUA (emergency use authorisation) labels. *Was changed to:* There are no interactions expected between approved COVID-19 vaccines and the use of BI 907828 monotherapy. Patients treated with BI 907828 should be carefully monitored for myelosuppressive side effects before COVID-19 vaccination is started as guided by the vaccine labels. Interactions with COVID-19 therapeutics cannot be excluded, and restrictions should be considered (Section 4.2.2.1).
Rationale for change		Based on the latest development of COVID-19 related vaccines and treatments.
Section to be changed		Section 2.1.1
Description of change		First bullet point for cohort 1 (biliary tract adenocarcinoma) was updated as follows: Cohort 1 aims to assess the efficacy, safety, and tolerability of BI 907828 monotherapy in patients with locally advanced or metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma. Patient must have received appropriate prior standard of care therapy or, in the opinion of the investigator be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy ~~or, patient prefers to~~

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		~~receive an MDM2-targeted therapy upfront instead of standard of care therapy~~.
Rationale for change		Correction of inconsistency with inclusion criteria.
Section to be changed		Sections 3.1 and 8.7
Description of change		"Final analysis" was updated to "primary analysis".
Rationale for change		Clarification
Section to be changed		Section 3.3.2
Description of change		1. Diagnosis of a solid tumour which meets the criteria for an open trial cohort: o Cohort 1 (biliary tract adenocarcinoma): Locally advanced or metastatic biliary tract adenocarcinoma (intra- and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer). Patient must have received appropriate prior standard of care therapy; or (in the opinion of the investigator) patient is unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. o Cohort 2 (pancreatic ductal adenocarcinoma): Locally advanced or metastatic pancreatic ductal adenocarcinoma. Patient must have received appropriate prior standard of care therapy. *Was changed to:* 1. Diagnosis of a solid tumour which meets the criteria for an open trial cohort: o Cohort 1 (biliary tract adenocarcinoma): Locally advanced or metastatic biliary tract adenocarcinoma (intra- and extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer). Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards; or (in the opinion of the investigator) patients are unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy. o Cohort 2 (pancreatic ductal adenocarcinoma): Locally advanced or metastatic pancreatic ductal adenocarcinoma. Patients must have unresectable

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		disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.
Rationale for change		Clarification
Section to be changed		Section 3.3.2
Description of change		2. Written pathology report / molecular profiling report indicating MDM2 amplification (copy number ≥8) and TP53 wild-type status. *Was changed to:* 2. Written pathology report / molecular profiling report indicating MDM2 amplification or a copy number ≥8, and TP53 wild-type status.
Rationale for change		Depending on laboratories, criteria to determine the MDM2 amplification are different, and more advanced criteria than just copy number reference may be used, especially in patients with di- or multiploidy genes.
Section to be changed		Section 3.3.3
Description of change		Exclusion criterion 16 was updated as follows: History or presence of cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure NYHA classification of ≥III or IV, unstable angina or poorly controlled arrhythmia which are considered as clinically relevant by the investigator. Myocardial infarction, stroke or pulmonary embolism within 6 months prior to ~~randomisation~~ the start of trial treatment.
Rationale for change		Correction of error
Section to be changed		Section 3.3.3
Description of change		Exclusion criterion 19 was added: Any of the following cardiac criteria: o Mean resting corrected QT interval (QTcF) >470 msec o Any clinically important abnormalities (as assessed by the investigator) in rhythm, conduction, or morphology of resting ECGs, e.g. complete left bundle branch block, third degree heart block o Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as

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		heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval (see also Section 4.2.2) o Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan).
Rationale for change		Potential effect of BI 907828 on QT prolongation has not been fully evaluated in humans
Section to be changed		Section 4.1.4.2 Guidance for dose delays due to other adverse events.
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Section 4.2.1.1
Description of change		Erythropoietin-stimulating agents (ESAs) should not be offered to most patients with non-chemotherapy-associated anaemia. Red blood cell transfusion may be an

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		option, depending on the severity of the anaemia or clinical circumstances (ASCO/ASH Clinical Practice Guideline Update 2019). *Was changed to:* Erythropoietin-stimulating agents (ESAs) can be offered to patients with treatment-associated anaemia. Red blood cell transfusion may be an option, depending on the severity of the anaemia or clinical circumstances.
Rationale for change		Clarification
Section to be changed		Section 4.2.1.2
Description of change		Recommendation about the prevention and treatment of gastrointestinal adverse event was updated – including change in duration, provision of reference documents, and format changes.
Rationale for change		The recommendation was reviewed with available guidelines.
Section to be changed		Section 4.2.2.1
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Section 4.2.2.1 and 10.1
Description of change		[redacted]
Rationale for change		

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Section to be changed		Section 4.2.2.1
Description of change		Following statement was added: Anti-viral treatments have recently been approved for use in some countries for the treatment of mild to moderate COVID-19 infection. [redacted]
Rationale for change		Based on the latest development of COVID-19 related treatments.
Section to be changed		Section 4.2.2.1
Description of change		Herbal preparations/medications are not allowed throughout the trial. These herbal medications include, but are not limited to St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications from 7 days prior to first dose of trial treatment until 30 days after the last dose of BI 907828. *Was changed to:* Herbal preparations/medications are allowed throughout the trial at the discretion of the investigator. Potential interactions described above should be taken into consideration.
Rationale for change		The wording in the first version was too general, but now the sponsor thinks that potential interactions should be checked on a case-by-case basis.
Section to be changed		Section 5.3.1
Description of change		Following statement was added: Plasma samples may be used for the measurement of unbound drug concentrations. For this purpose, pooled plasma samples may be used. Results may be included in a separate report.
Rationale for change		Clarification was made for the provision of additional information regarding the use of samples.
Section to be changed		Section 5.4
Description of change		Following statement was added:

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		Planned exploratory analyses of biomarkers during the trial may be reduced or stopped based on new information in the literature or early analyses.
Rationale for change		Clarification
Section to be changed		Section 5.4.2.1
Description of change		Following statement was removed: As testing of MDM2 amplification and TP53 status is conducted retrospectively for patients deemed eligible per local testing, if test results are inconsistent, the investigator will be informed, and the patient will continue at the investigator's discretion, taking into consideration the patient's clinical benefit.
Rationale for change		The central test for MDM2 and TP53 is still considered experimental, and it is not for medical decision making. Moreover, test results will only be available when clinical benefit has already been measured.
Section to be changed		Section 5.6.2
Description of change		Following statement was removed: During the conduct of the trial, the sponsor may decide to implement paper questionnaires.
Rationale for change		It was confirmed to be logistically impossible.
Section to be changed		Section 6.2.1
Description of change		The underlined parts were added: • Primary tumour site <u>(including subsite information, e.g., for biliary tract cancer, subsites include intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullar cancer)</u> (…) • Previous anti-cancer treatments including any surgery, radiotherapy, and or systemic therapy, including start and end dates as well as the outcome. <u>If available, the last 2 tumour scans prior to baseline in this trial should be uploaded to the central image repository.</u>
Rationale for change		First one is for clarification. Second one is to understand the trend of disease status before the trial participation as aggregated population. This will allow to put the efficacy data into context, as there are cases reported of patients with a slow growing tumour.

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Section to be changed		Section 6.2.4
Description of change		The underlined part was added: In case of continued clinical benefit judged by the investigator (e.g., absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites [e.g., CNS metastasis, respiratory failure due to tumour compression, spinal cord compression] requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment), and based on careful clinical assessment, patients may be allowed to continue BI 907828 beyond disease progression as defined by RECIST version 1.1 criteria.
Rationale for change		Clarification
Section to be changed		Section 8.7
Description of change		"a statistician" was removed from the DMC members composition.
Rationale for change		This trial is designed as a single arm trial with no blinding, so the internal trial statistician can provide necessary information directly to the DMC physicians if needed.
Section to be changed		Section 9.1
Description of change		P22-02579, P22-05918, and P22-05968 were added.
Rationale for change		To provide available reference guidelines about prevention and treatment of gastrointestinal adverse events.
Section to be changed		Section 10.1
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		Section 10.2
Description of change		Visit allowance was updated for some visits. Time point of 12-lead ECG from cycle 5 onwards was updated from -0:05 to 4:00. PK -0:05 time point was added.
Rationale for change		Visit allowance: Inconsistency with the main flowchart. ECG: To make it consistent with the earlier cycles. PK: Correction of error.

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11.2 GLOBAL AMENDMENT 2

Date of amendment		14 Jan 2023
EudraCT number **EU number**		2022-001500-18
BI Trial number		1403-0011
BI Investigational Medicinal Product(s)		BI 907828
Title of protocol		Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of BI 907828 for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page
Description of change		Revised lay title: A study to test whether BI 907828 helps people with cancer in the biliary tract ~~or~~, pancreas**, lung, or bladder**
Rationale for change		Based on the data from Phase I trials, the sponsor decided to add cohorts for lung cancer and urothelial bladder cancer.
Section to be changed		Synopsis
Description of change		New cohorts added and necessary changes implemented.
Rationale for change		Based on the data from Phase I trials, the sponsor decided to add cohorts for lung cancer and urothelial bladder cancer.
Section to be changed		Flowchart
Description of change		Patient-reported outcome measures for the new cohorts added.
Rationale for change		Due to addition of new cohorts
Section to be changed		1.1
Description of change		Medical background for the new cohorts added.
Rationale for change		Due to addition of new cohorts
Section to be changed		1.2
Description of change		Data from clinical studies updated based on the most recent IB update (DLP 16 Sep 2022).
Rationale for change		Release of an updated version of the IB
Section to be changed		2.1.1
Description of change		Main objectives for the new cohorts added.

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Rationale for change		Due to addition of new cohorts
Section to be changed		2.2.2
Description of change		Further endpoints reflecting patient-reported outcomes modified to include the new cohorts.
Rationale for change		Due to addition of new cohorts
Section to be changed		3.1
Description of change		Updated trial design description and trial design figure to reflect the new cohorts.
Rationale for change		Due to addition of new cohorts
Section to be changed		3.2
Description of change		New text added to describe the standard treatment for the new cohorts.
Rationale for change		Due to addition of new cohorts
Section to be changed		3.3
Description of change		Text updated to reflect new cohorts: The total number of planned patients in this trial is **130** patients (90 patients in Cohort 1, 10 patients in Cohort 2, **and 15 patients in Cohorts 3 and 4.**)
Rationale for change		
Section to be changed		3.3.2, inclusion criterion 1
Description of change		New text added: ○ **<u>Cohort 3 (lung adenocarcinoma):</u> Locally advanced or metastatic lung adenocarcinoma. Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.** ○ **<u>Cohort 4 (urothelial bladder cancer):</u> Locally advanced or metastatic urothelial bladder cancer. Patients must have unresectable disease and have received all available conventional therapies known to confer clinical benefit for their disease based on local approved standards.**
Rationale for change		Due to addition of new cohorts
Section to be changed		3.3.2, inclusion criterion 2
Description of change		New text added: Written pathology report / molecular profiling report indicating MDM2 amplification or a copy number ≥8, and TP53 wild-type status. **This must have been confirmed with a tissue-based test. A test with liquid biopsy is not accepted.**
Rationale for change		Clarification

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Section to be changed		3.3.3, exclusion criterion 10
Description of change		Viral load >400 copies/**mL** ~~µL~~(local laboratory assessment)
Rationale for change		Correction of an error
Section to be changed		3.3.3 exclusion criterion 20
Description of change		New criterion was added: 20. Patients who cannot swallow pills.
Rationale for change		Clarification
Section to be changed		5.3.2
Description of change		A description about the use of samples for methodological investigations was added.
Rationale for change		Clarification
Section to be changed		5.4.2
Description of change		Text modified to now read: Tumour samples will be used for the retrospective testing of MDM2 amplification and TP53 status. **They will be used for co-development of a companion diagnostic test.** [redacted] If the molecular pathology test for eligibility has been performed by a vendor designated by the sponsor **using the same test as the one used for development of the diagnostic test,** the submission of a tissue sample is not required.
Rationale for change		Clarification
Section to be changed		5.6.2
Description of change		Information on patient-reported outcomes questionnaires for the new cohorts added.
Rationale for change		Due to addition of new cohorts
Section to be changed		7 and its subsections
Description of change		New cohorts added to the planned analyses; new questionnaires for patient-reported outcomes included.
Rationale for change		Due to addition of new cohorts
Section to be changed		9.1
Description of change		New references added: R14-3261, R16-1875, R16-5828, R22-4066, R22-4068
Rationale for change		New text added to sections 1.1 and 3.2.
Section to be changed		9.2
Description of change		Updated reference for the IB 1403-P0X

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Rationale for change		IB update with DLP 16 Sep 2022
Section to be changed		10.1
Description of change		[redacted]
Rationale for change		Based on the latest information/assessment
Section to be changed		10.2
Description of change		The window for 8-hour time point was updated from ±10 min to ±30 min.
Rationale for change		A larger window was considered acceptable.

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11.3 GLOBAL AMENDMENT 3

Date of amendment		19 Jun 2023
EudraCT number **EU number**		2022-001500-18
BI Trial number		1403-0011
BI Investigational Medicinal Product(s)		Brigimadlin (BI 907828)
Title of protocol		Brightline-2: A Phase IIa/Iib, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		General
Description of change		BI 907828 replaced with brigimadlin
Rationale for change		Brigimadlin, the international nonproprietary name, has become available.
Section to be changed		Title page, synopsis
Description of change		New contact information for the coordinating investigator. Universal trial number was added.
Rationale for change		Contact information has changed. Universal trial number was obtained.
Section to be changed		Synopsis
Description of change		New cohort added (Cohort 1-CN; 25 patients), overall patient number increased (from 130 to 155), MDM2 amplification criterion updated to match the updated criterion in section 3.3.2, statistical method for Cohort 1-CN added.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		Flowchart (table)
Description of change		Time window for Day 1 (Cycle 2 onwards) was modified to ±3 d. Consistent use of ‘d’ instead of ‘days’. Specific entries which assessments are needed for Cohort 1-CN (EORTC QLQ-BIL21) or are not needed (plasma samples for circulating proteins; fresh tumour biopsy).
Rationale for change		Time intervals allow for more flexibility; the new Cohort 1-CN requires specific assessments.

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Section to be changed		Flowchart (footnotes)
Description of change		Footnote #1 was modified to read (new text is indicated in bold) "**A cycle is** 21 days **(±3 days)** in duration and may be extended if subsequent dosing is delayed e.g. due to toxicity. **An interval of 18-24 days between doses must be maintained throughout, unless criteria for delaying treatment are met.** (…)"
Rationale for change		Allow for more flexibility.
Section to be changed		Abbreviations and definitions
Description of change		Minor corrections.
Rationale for change		Errors corrected; missing entries added.
Section to be changed		1.1
Description of change		Cohort 1-CN added. Minor corrections.
Rationale for change		A cohort for patients from mainland China only was added to the trial. Typos and minor errors corrected.
Section to be changed		1.2
Description of change		Key pharmacokinetic characteristics, drug interactions, and data from clinical studies updated based on new information in the Investigator's Brochure (IB).
Rationale for change		New information available with the updated IB.
Section to be changed		1.3
Description of change		New paragraph added: "Patients in mainland China are enrolled in a separate cohort (Cohort 1-CN) because separate analyses are required for mainland China and rest of the world populations. A separate CDx development will be pursued for mainland China, as it is not feasible to export human tissue samples from China to the appointed global laboratory for CDx development. Instead, a laboratory located in China will perform the central laboratory analyses for patients enrolled in China (confirmation of MDM2 and TP53 status)."
Rationale for change		Description of the special requirements for China.
Section to be changed		1.4.2
Description of change		Risks section was updated to read "brigimadlin has been administered to **more than 170** patients in ongoing clinical trials.".
Rationale for change		New information available with the updated IB.
Section to be changed		2.1.1
Description of change		Main objectives for Cohort 1-CN added.
Rationale for change		A cohort for patients from mainland China only was added to the trial.

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Section to be changed		2.1.3, 2.2.2
Description of change		Cohort 1-CN added.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		3.1
Description of change		New overall trial design figure added. Descriptive text below the figure modified to reflect the new cohort and to summarize patient recruitment into this new cohort.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		3.2, 3.3
Description of change		Changes to number of sites and overall patient number to add the new cohort.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		3.3.2
Description of change		Inclusion criterion #1 modified to read "(…) Cohort**s** 1 **and 1-CN** (biliary tract adenocarcinoma) (…). Table 1 entry about coagulation modified to read "≤1.5×institutional ULN **unless on a stable dose of an anticoagulant with no unexplained elevation of INR**".
Rationale for change		A cohort for patients from mainland China only was added to the trial. Allow for exemptions.
Section to be changed		3.3.2, 5.4.2.1
Description of change		Inclusion criterion #2 modified to require MDM2 copy number ≥8 unless the molecular pathology test has been performed by a laboratory designated by the sponsor for development of the companion diagnostic test.
Rationale for change		To mitigate the risk of discordant results between local and central tests.
Section to be changed		3.3.3
Description of change		Exclusion criterion #11 modified to read "Patients with a history of HCV infection who meet 1 or **more** of the following criteria: (…) **Not yet achieved sustained viral response (SVR)** (…). #19 modified to read: "(…) Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years-of-age~~., or any~~

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		~~concomitant medication known to prolong the QT~~ interval", "(…) Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). **A historic measurement of EF no older than 6 months prior to first administration of trial drug can be accepted provided that there is clinical evidence that the patient's cardiac disease has not significantly worsened since this measurement in the opinion of the Investigator or of the treating physician or both.**"
Rationale for change		Sustained viral response is needed for trial participation. Concomitant medication related info already covered in exclusion criterion 5 and Section 4.2.2.1. Allow for more flexibility.
Section to be changed		4.1.1, 4.1.4.2
Description of change		[redacted]
Rationale for change		
Section to be changed		4.1.4.1
Description of change		One of the criteria to administer brigimadlin was updated: Platelet count is ≥100×10^9/L (In case of platelet transfusion after the last drug administration, this criterion must be met in at least two subsequent measurements that are at least 48 hours apart)
Rationale for change		Clarification
Section to be changed		4.1.6
Description of change		Reasons for not having some of the information on the label were added.
Rationale for change		Clarification
Section to be changed		4.2.1.1

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Description of change		The required interval between the screening laboratory assessment and the last transfusion was changed from 4 weeks to 2 weeks
Rationale for change		2 weeks interval was deemed sufficient for appropriate screening assessment.
Section to be changed		4.2.1.2
Description of change		The anti-emetic prophylaxis was made mandatory. New sentence added: “In addition, anti-diarrheal agents are recommended in accordance with international and local guidelines.”
Rationale for change		Further guidance for the investigator.
Section to be changed		4.2.1.3
Description of change		New bullet point added: “Local therapy (radiotherapy, surgery, ablation) of target lesions should be avoided wherever possible. If local therapy is given, the treated area cannot be used for further tumor response assessment. Further treatment must be agreed between the sponsor and the investigator.”
Rationale for change		Further guidance for the investigator.
Section to be changed		4.2.2.1
Description of change		Restrictions on other anti-cancer therapies added.
Rationale for change		Clarification
Section to be changed		4.2.2.1
Description of change		[redacted]
Rationale for change		New information available with the updated IB.
Section to be changed		4.2.2.1

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Description of change		Instructions on medications known to prolong the QT interval added.
Rationale for change		Originally included in Section 3.3.3, but Section 4.2.2.1 was considered more appropriate.
Section to be changed		5.2.3
Description of change		CK-MB was removed
Rationale for change		It was concluded that CK-MB was not required provided that troponin is measured when CK is elevated.
Section to be changed		5.2.6.1.4
Description of change		Fatigue removed from AESI.
Rationale for change		Based on the data, it was considered no longer particular concern for prospective safety monitoring.
Section to be changed		5.4.2.1
Description of change		Clarifications and exemption of Cohort 1-CN from the optional fresh tumour biopsy.
Rationale for change		Clarification.
Section to be changed		5.4.3
Description of change		[redacted]
Rationale for change		These are covered in section 5.4.5.
Section to be changed		5.4.5, 5.4.7, 5.4.8
Description of change		Exemption of Cohort 1-CN from the analyses of circulating proteins. Removal of the paragraph “Samples taken to determine modulation of GDF-15, CA 19-9, and CEA will be used to describe the PK/PD relationship. Details of time points for sample collection are specified in the Flowchart. CA19-9 and CEA are tested locally.” The content was moved to new dedicated subsections 5.4.7 and 5.4.8.
Rationale for change		Clarification.
Section to be changed		5.6.2, 6.2.1
Description of change		Cohort 1-CN added.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		6.1

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Description of change		Description about routine safety laboratory tests at a remote facility added.
Rationale for change		To allow more flexibility and convenience for patients, particularly when patients are waiting for recovery from haematological AEs.
Section to be changed		7 and its subsections
Description of change		Adaptations and new text blocks due to the introduction of the new Cohort 1-CN.
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		8.6
Description of change		New definition added: "The end of the trial for Cohort 1-CN is defined as the timepoint when all patients treated in Cohort 1-CN have ended treatment, have completed (or failed to attend) the FU for safety visit, and have been followed up for at least 6 months on survival status or have died before.".
Rationale for change		A cohort for patients from mainland China only was added to the trial.
Section to be changed		10.1
Description of change		Examples of restricted concomitant medications updated.
Rationale for change		New information available.
Section to be changed		10.2
Description of change		Time windows modified.
Rationale for change		Consistency with the flowchart.

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11.4 GLOBAL AMENDMENT 4

Date of amendment		07 May 2024
EU number		2023-506369-79-00
BI Trial number		1403-0011
BI Investigational Medicinal Product(s)		Brigimadlin (BI 907828)
Title of protocol		Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Title page, synopsis**
Description of change		Change from: EudraCT No. 2022-001500-18 To: EU CT Number 2023-506369-79-00
Rationale for change		Updated EU Regulation
Section to be changed		**Title page**
Description of change		[redacted]
Rationale for change		New CTL contact details
Section to be changed		**Flowchart (Footnote 2), 6.2.3.1**
Description of change		Addition of: If the decision to permanently discontinue is made >35 days after dosing (i.e. following a dose delay) the FU for Safety visit will take place as

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		soon as possible but will be >35 days after last dose. In this situation the EOT visit and the FU for Safety visit may be combined.
Rationale for change		Further guidance
Section to be changed		**Flowchart (Footnote 13)**
Description of change		Change from: …the detailed sampling schedule is available in Appendix 10.2. To: …the detailed sampling schedule for *PK and GDF-15* is available in Appendix 10.2. *For all other biomarkers, sampling must be done at the day of the visit, ideally before drug administration.*
Rationale for change		Clarification
Section to be changed		**Flowchart (Footnote 18), 3.3.4.1, 5.1.1, 6.2.3.3**
Description of change		Change from: disease progression To: *objective* disease progression
Rationale for change		Clarification
Section to be changed		**1.1**
Description of change		Change from: Currently, patients with biliary tract cancers receive 1st line chemotherapy (with or without checkpoint inhibitor), and 2nd line chemotherapy if the patient's condition allows. The benefit of 2nd line chemotherapy is modest, with a median overall survival (OS) of 6 months and an overall response rate (ORR) of 5% (ABC-06 trial [R22-0948]). To: The combination durvalumab, or pembrolizumab in certain circumstances, with gemcitabine + cisplatin chemotherapy is the standard 1st line treatment for patients with BTC [R24-1181; R23-1555]. The benefit of 2nd line FOLFOX chemotherapy is modest, with an mOS of 6 months, a median progression-free survival (mPFS) of 4 months, and an objective response rate (ORR) of 5% as shown in the ABC-06 trial, which recruited in the UK [R22-0948]. A randomized Korean Phase II trial showed an mOS of 6.3 months, a mPFS of 2.8 months, and an ORR of 5.9% [R24-0991].
Rationale for change		To update the current SoC information

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Section to be changed		**1.1**
Description of change		Update of clinical trial landscape and ongoing brigimadlin trials
Rationale for change		Availability of new data
Section to be changed		**1.2**
Description of change		Change from: The MDM2-p53 antagonist brigimadlin (also known as BI 907828) is a small molecule that inhibits the interaction between the tumor suppressor TP53 and its negative regulator MDM2. To: The MDM2-p53 antagonist brigimadlin (also known as BI 907828) is a small molecule that binds the mouse double minute 2 homolog protein (MDM2) and inhibits its interaction with the tumor suppressor p53.
Rationale for change		Clarification
Section to be changed		**1.2**
Description of change		Update of Key pharmacokinetic characteristics
Rationale for change		Availability of new data
Section to be changed		**1.2**
Description of change		[redacted]
Rationale for change		Availability of new data
Section to be changed		**1.2**
Description of change		Addition of: [redacted]
Rationale for change		Availability of new data
Section to be changed		**1.2**
Description of change		Update of Data from non-clinical studies
Rationale for change		Availability of new data
Section to be changed		**1.2**
Description of change		Update of Data from clinical studies
Rationale for change		Availability of new data
Section to be changed		**1.4.1**

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Description of change		[redacted]
Rationale for change		Availability of new data
Section to be changed		**1.4.2**
Description of change		Change from: more than 170 patients To: more than 750 patients
Rationale for change		Availability of new data
Section to be changed		**1.4.2**
Description of change		[redacted]
Rationale for change		Availability of new data
Section to be changed		**1.4.2**
Description of change		[redacted]
Rationale for change		Update of safety information
Section to be changed		**3.3**
Description of change		Addition of text regarding recruitment of a representative patient population
Rationale for change		Ensures that the trial will be conducted in a population that is representative of patients who will ultimately use the medication
Section to be changed		**3.3.2 (Table 1)**
Description of change		Change from: ≤3×upper limit of normal (ULN) To: ≤1.5×upper limit of normal (ULN), (patients with Gilbert's syndrome, total bilirubin must be ≤3×ULN)
Rationale for change		Available data suggest that patients with high total bilirubin value at baseline have a relatively worse safety profile
Section to be changed		**3.3.2 (Table 1)**
Description of change		Addition of "AND" for coagulation parameters
Rationale for change		Clarification
Section to be changed		**3.3.3**
Description of change		Change from: major infection To:

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		severe infection
Rationale for change		Update of guidance
Section to be changed		**4.1.4.1**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**4.1.4.1, 4.1.4.2**
Description of change		Addition of: (except for haemoglobin, where the patient must recover to ≥8.0 g/dL or ≥4.9 mmol/L or ≥80 g/L).
Rationale for change		Further specification needed
Section to be changed		**4.1.4.1, 4.2.2.2**
Description of change		Change from: For all treatment cycles, food should not be consumed for at least 2 h before brigimadlin administration and at least 1 h after brigimadlin administration. To: Brigimadlin can be taken with or without food
Rationale for change		Update of guidance
Section to be changed		**4.1.4.2**
Description of change		Change from: Platelet and neutrophil count are assessed on Day 1 (or within 72 h prior to) each treatment cycle. To: Platelet and neutrophil count are assessed on the **planned** Day 1 of (or within 72 h prior to) each treatment cycle. **Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle.**
Rationale for change		Clarification
Section to be changed		**4.1.4.2 (Figure 2)**
Description of change		Update of Figure 2 (Algorithm for treatment pauses of brigimadlin based on low platelet count and/or low neutrophil count) and footnotes
Rationale for change		Update of guidance
Section to be changed		**4.1.4.2**
Description of change		Addition of:

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		Recovery days and treatment pause should be counted from the planned Day 1 of the treatment cycle
Rationale for change		Clarification
Section to be changed		**4.2.1.1**
Description of change		Addition of text regarding guidance on severe neutropenia
Rationale for change		Update of guidance
Section to be changed		**4.2.1.1**
Description of change		Addition of text regarding guidance on severe cytopenia lasting more than 2 months
Rationale for change		Update of guidance
Section to be changed		**4.2.1.1**
Description of change		Change from: High-risk features include expected prolonged (>10 days) and profound (<0.1 × 10^9/L)… To: High-risk features include expected *or observed* prolonged (>*7* days) and profound (<0.1 × 10^9/L)…
Rationale for change		Update of guidance
Section to be changed		**4.2.1.1**
Description of change		Removed: In case of long-lasting thrombocytopenia (i.e. no recovery to ≥75.0×10^9/L after at least 4 weeks from the nadir), a haematology workup should be considered at the investigator's discretion including bone marrow cytology, platelet volume, and haematologist advice for appropriate therapy and follow-up.
Rationale for change		Update of guidance
Section to be changed		**4.2.1.1**
Description of change		Change from: There must be at least 2 weeks between a patient's last transfusion… To: There must be at least 1 week between a patient's last transfusion…
Rationale for change		Update of guidance
Section to be changed		**4.2.2.1, 10.1 (Table 8)**
Description of change		Addition of allowance of topical preparations of restricted medications
Rationale for change		Update of guidance
Section to be changed		**4.2.2.1**
Description of change		[redacted]

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		[redacted]
Rationale for change		Update of guidance
Section to be changed		**4.2.2.1**
Description of change		[redacted]
Rationale for change		Update of guidance

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Section to be changed		**4.2.2.1**
Description of change		Change from: the following concomitant medications prohibited: To: the following concomitant medications should be handled as follows:
Rationale for change		Clarification
Section to be changed		**4.2.2.3**
Description of change		Addition of: two medically approved methods of birth control, including
Rationale for change		Update of guidance
Section to be changed		**4.2.2.3**
Description of change		Addition of: The efficacy of oral hormonal contraceptives may be compromised by vomiting and/or diarrhoea or other conditions where the absorption may be affected. Women taking oral hormonal contraceptives and experiencing these conditions should be advised to use an alternative highly effective contraceptive measure.
Rationale for change		Update of guidance
Section to be changed		**5.1.1**
Description of change		Change from: unless the lesions occurred after irradiation To: unless the lesions occurred or progressed after irradiation
Rationale for change		Clarification
Section to be changed		**5.2.3, Table 2**
Description of change		Change from: (CK; if CK is elevated, then *Troponin I or T and myoglobin should be reactively tested).* To: (CK; if CK is elevated, then *patient should be further evaluated according to local standard of care).*
Rationale for change		Update of guidance
Section to be changed		**5.2.6.1.4**
Description of change		Change from: In this trial, hepatic injury, hematological AEs, gastrointestinal AEs… To: In this trial, hepatic injury, *specified* hematological AEs, *specified* gastrointestinal AEs…

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Rationale for change		Clarification
Section to be changed		**5.6.1, 6.2.1**
Description of change		Addition of text requiring smoking history to be collected for Cohort 3
Rationale for change		Update of required data to be collected
Section to be changed		**8**
Description of change		Change from: the EU directive 2001/20/EC / EU Regulation 536/2014 To: EU Regulation 536/2014
Rationale for change		Updated EU Regulation
Section to be changed		**8.7**
Description of change		Addition of: In EU/EEA countries, the trial is sponsored by Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.
Rationale for change		The clinical trial regulation requires trial protocol to state trial sponsor name and address, but the current protocol template does not include the information.
Section to be changed		**10.1 (Table 8)**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**10.1 (Table 8)**
Description of change		[redacted]
Rationale for change		Update of guidance
Section to be changed		**General**
Description of change		List of abbreviations and references were updated; typos were removed, and grammar was corrected.
Rationale for change		Improve the readability of the document.

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11.5 GLOBAL AMENDMENT 5

Date of amendment		04 Feb 2025
EU number		2023-506369-79-00
BI Trial number		1403-0011
BI Investigational Medicinal Product(s)		Brigimadlin (BI 907828)
Title of protocol		Brightline-2: A Phase IIa/IIb, open-label, single-arm, multi-centre trial of brigimadlin (BI 907828) for treatment of patients with locally advanced / metastatic, MDM2 amplified, TP53 wild-type biliary tract adenocarcinoma, pancreatic ductal adenocarcinoma, or other selected solid tumours
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**Synopsis (number of patients per treatment group), 7.5**
Description of change		Addition of: In November 2024, Boehringer Ingelheim decided to discontinue future development of brigimadlin. Recruitment in 1403-0011 and further expansion of the study, including Cohort-1-CN has been discontinued as of 26 Nov 2024.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**Flowcharts**
Description of change		Reduced schedule flowchart was added; previous flowchart is no longer applicable
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**1**
Description of change		Text added to summarize changes made in Global Amendment 5
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**3.3.4.1**
Description of change		Change from: The patient should attend all remaining visits. This includes the follow-up for disease progression assessments if a patient discontinued treatment prior to documented objective disease progression and did not start subsequent anti-cancer treatment. To: The patient should attend all remaining visits as outlined in the reduced schedule Flowchart,

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		which no longer includes follow-up for disease progression. Prior to Global amendment 5, this included the follow-up for disease progression assessments if a patient discontinued treatment prior to documented objective disease progression and did not start subsequent anti-cancer treatment.
Rationale for change		Added for clarity
Section to be changed		**3.3.4.1**
Description of change		Change from: After completion of the final OS analysis (see Section 7) To: As of Global Amendment 5.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**3.3.4.1**
Description of change		Addition of: If a patient receives brigimadlin in another clinical trial, safety follow-up in this trial will end, and safety follow-up will continue uninterrupted in the new trial.
Rationale for change		Added for clarity
Section to be changed		**4.1.6**
Description of change		Updates to details regarding the “Investigator Name” and “Visit Number” Addition of: The address and telephone number of the main contact was omitted from the label…
Rationale for change		Updated per regulation requirements
Section to be changed		**5.1.1**
Description of change		Addition of: As of Global Amendment 5, imaging-related endpoints will no longer be assessed by central independent review.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**5.2.6.2.1**
Description of change		Addition of: If a patient receives brigimadlin in another clinical trial, safety follow-up in this trial will end, and safety follow-up will continue uninterrupted in the new trial.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**5.3**
Description of change		Addition of: As of Global Amendment 5, sampling and analyses for pharmacokinetics of brigimadlin will be discontinued; this section is no longer applicable.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**5.4**

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Description of change		Addition of: As of Global Amendment 5, analyses of exploratory biomarkers will be discontinued; this section is no longer applicable.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**5.6.2**
Description of change		Addition of: As of Global Amendment 5, patient-reported outcome questionnaires will be discontinued; this section is no longer applicable.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**6.1**
Description of change		Change from: During the treatment phase, visits should be performed weekly during Cycles 1 and 2, and once or twice per cycle (as indicated in the Flowchart) from Cycle 3 onwards, within 2 days of the scheduled date. To: During the treatment phase, visits should be performed as indicated in the Flowchart.
Rationale for change		Updated to reflect updated schedule
Section to be changed		**6.2.3.3**
Description of change		Addition of: As of Global Amendment 5, patients will continue to be followed up for safety as described in Section 5.2 but after treatment discontinuation will no longer be followed up for disease progression and overall survival.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**7.1**
Description of change		Addition of: Hypothesis testing will no longer be conducted as a result of the decision to discontinue development of brigimadlin.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**7.2.1, 10.2**
Description of change		Addition of: **“**no longer applicable as of Global Amendment 5”
Rationale for change		Updated due to the decision to discontinue development of brigimadlin
Section to be changed		**7.2.3**
Description of change		The duration of SD was changed from 42 to 35 days.
Rationale for change		Updated due to the decision to discontinue development of brigimadlin

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Section to be changed		**7.2.3**
Description of change		Deletion of: The one-sided p-value will be generated from the one-sample proportion test (exact method).
Rationale for change		Hypothesis testing will no longer be conducted as a result of the decision to discontinue development of brigimadlin.
Section to be changed		**Title page, Synopsis, Abbreviations**
Description of change		New document number, new abbreviation
Rationale for change		Administrative updates

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